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Editors

Clinical Neuro-Ophthalmology

DVD ROM

A Practical Guide

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Springer

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A Practical Guide

Foreword by William F. Hoyt
Translation by William Hart

With 184 Figures in 357 parts,
75 Tables, 5 Posters and DVD

Springer

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Dedication

We gratefully dedicate this work to our
(neuro-) ophthalmic role models and mentors:

Elfriede Auhlhorn,
Heinrich Harms,
Bernard Becker,
and
Ronald M Burde

And to our lives' companions Monika, Barbara, and Mary

Foreword

This English version of the 2003 primer *Praktische Neuroophthalmologie* should be welcomed worldwide by students of ophthalmology. It is beautifully illustrated in color, clearly written, and, best of all, supplemented with an interactive DVD with video clips.

The text is loaded with "Pearls," specifically marked for the reader's attention.

Several modest-sized books published in the past 10 years have attempted to cover the complicated subject of neuro-ophthalmology in a manageably brief format. This German effort joins the competition, with the distinct advantage of a DVD.

Professors Schiefer, Wilhelm, and Hart, along with 23 coauthors, have my congratulations and admiration for a thoughtful, handsome job well done.

William F. Hoyt, MD, Professor Emeritus
University of California, San Francisco

Preface

Yet another textbook of clinical neuro-ophthalmology?

This text and its digital supplement are meant to be used by comprehensive ophthalmologists and residents in training, and are not meant to be used as one would the larger, almost encyclopedic, reference texts with their detailed citations and case reports. Resident physicians should find the format of this text particularly helpful as a learning tool, including the interactive, digital (DVD) supplement. The material is sufficiently complete as to allow a global perspective of the material, and yet it remains sufficiently brief that the entire volume can be consumed in a few weeks, rather than in months or years. The use of colored illustrations should be particularly valuable for those being introduced to the broad spectrum of clinical findings, especially those that portray the varied appearances of the optic disc and retina. Video clips also provide a compelling demonstration of the subtle elements of ocular and pupillary movements.

Acknowledgements

The editors are particularly grateful for the efforts of the authors, who were tasked with the goal of covering each of their subjects from a global perspective while keeping the chapters as brief as reasonably possible. The authors, in turn, wish to express their gratitude for the tireless efforts of the editorial staff at Springer Verlag, above all, the contributions of Marion Philipp and Martina Himberger, as well as Judith Diemer from LE-TeX. The editors also gratefully acknowledge the generous permission granted by Dr. Reinhard Kaden for the use of an English-language translation taken from the original German text *Praktische Neuro-ophthalmologie,* U. Schiefer, H Wilhelm, E. Zrenner, and A. Burk (eds) (2003) Kaden Verlag, Heidelberg, Germany.

The authors and editors are also indebted to Regine Gattung-Petith, Albert R. Gattung, Alexander Lorenz, Maja Grigoleit, Regina Hofer, and Jan Schiller for their support, advice, and production of numerous figures, graphic elements, and video animations. Maja Grigoleit is specifically acknowledged for her design of the graphic elements used in the interactive case management vignettes. Heartfelt gratitude is also expressed for the contributions and support of those at Pharm-Allergan, Ettlingen, and especially of Dr. Friedemann Kimmich, whose generous support allowed preparation of the interactive version. Dr. Simon Wiest is especially acknowledged for his advice and assistance during preparation of the interactive DVD companion to the text.

The editors and authors thank the many patients for their patience and cooperation during collection of the case material, and for allowing their neuro-ophthalmological disorders to be recorded in written, graphic, and video formats. The translator is indebted to the many authors for gracious consent in allowing the translated version to avoid the use of literal interpretations in favor of explanatory clarity. Finally, the editors are truly indebted to their families, above all their wives, Monika, Barbara, and Mary, for their unflagging support and encouragement over the past 3 years.

Readers who use this work are encouraged to give us feedback regarding missing, ambiguous, erroneous, and/or confusing elements, allowing us to further improve the work during production of subsequent editions. We hope that readers will enjoy some of the unique features to be found in both the written and interactive portions of the work, and that our ophthalmic colleagues will find this material helpful for both the learning and the teaching of the subject.

Ulrich Schiefer
Helmut Wilhelm
William Hart
Tübingen, February 2007

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Chapter 1

The Initial Encounter: Taking a History and Recognition of Neuro-Ophthalmic Emergencies

U. Schiefer and H. Wilhelm

Ninety percent of clinical neuro-ophthalmology is in the taking of a history (after W.F. Hoyt). Attentive listening, specific questioning and careful evaluation of the information gained make up the foundation of what is primarily a diagnostic subspecialty. The effort invested in gathering this information saves time and avoids unnecessary, potentially dangerous and/or expensive diagnostic procedures.

History Taking

When possible, the previous records of the patient's care should be reviewed prior to beginning the interview. Usually, if the patient will allow, it helps to include in the conversation those other persons who have come to the visit, such as the patient's spouse or close relatives. These people can often provide information that the patient does not know or cannot remember. Patients are often anxious or fearful, and the physician can put them more at ease by conversing in layperson's terms rather than in the technical jargon used by clinicians.

When caring for children, the history taken from one or both parents should not take too long, as the success of the ensuing examination may be hampered by the impatience of the child. When necessary, one should defer some of the more detailed questioning until after the examination has been completed.

The proposed schema for historical questioning, given in ■ Table 1.1, provides a rough outline of the more common details to be discussed, and those that can be compressed or expanded, depending on the details of the case.

When taking the current ophthalmic history, it is of particular importance to determine as precisely as possible the point in time and the speed with which the initial symptoms presented. The longer it has been since the onset of symptoms and the more slowly they may have developed, the more difficult it will be to obtain this information. One should also obtain an accurate account of the eliciting factors, the temporal relationships, accompanying symptoms, and subsequent course of events. Knowledge of these details will allow a quick initial recognition of the more likely sources and various classes of neuro-ophthalmic disease (■ Fig. 1.1).

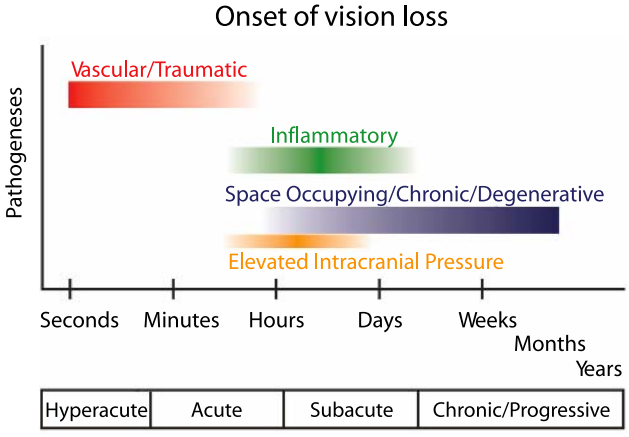


Fig. 1.1. Characteristic onsets and courses of neuro-ophthalmically relevant clinical syndromes

Neuro-Ophthalmic Emergencies

From the very start of history taking, one should be alert for clues to the presence of potentially life-threatening or catastrophically blinding disorders. The disorders in this category are listed in ■ Table 1.2, which also gives corresponding references to the appropriate chapters and sections of this text.

Further Reading

Purvin V, Kawasaki A (2005) Neuro-ophthalmic emergencies for the neurologist. Neurologist 11: 195–233

Table 1.1. Catalog of queries to consider when taking a neuro-ophthalmic history

Current ophthalmic history:

- Current symptoms: time and date of onset, inciting factors, course since onset
- Symptoms experienced during the encounter
- Associated symptoms of a general (nonvisual) nature
- Management of the problem to date

Comprehensive ophthalmic history (questions appropriate to the time of onset and the patient's age):

- For children: Do both eyes see equally well? Does the child have a lazy eye, or has an eye ever been patched for more than a day?
- At what age were glasses first needed, and what visual problem(s) required glasses?
- Since what age have contact lenses been used? Are they hard, semirigid, or soft?
- Has there ever been a problem with eye alignment?
- Has there been any ocular surgery? Eye injuries? Periods of ocular pain and redness?
- Has one or both eyes ever had elevated pressures? Has there been a diagnosis of glaucoma?
- Has there ever been a diagnosis of cataract?
- Is there a congenital color deficiency (for male patients)?
- Have there been other problems: loss of peripheral vision? A disturbance of reading? Photophobia? Poor dark adaptation? Problems understanding visual images?
- Ophthalmic medications? Eye drops?

Family history of eye disease? Birth defects?

- Have there ever been any severe, inherited eye diseases in the family?
- Very poor vision? Strabismus? Cataract? Retinal detachment? Elevated eye pressures? Glaucoma? Poor color vision? Optic atrophy? Blindness? Macular degeneration? Poor reading even with glasses in elderly family members?

General medical history (depending on time of onset and/or the patient's age):

- Systemic diseases: Heart? Lungs? Liver? Kidneys? GI tract? Brain? Vascular disease? Tumors?
- Operations? Hospital admissions? Accidents? Injuries?
- Metabolic disorders: high blood sugar? Overactive thyroid gland? High cholesterol? Gout?
- Hypertension?
- Tobacco, alcohol, and/or recreational drug use?
- Allergies?
- Medications? (Particularly important!)

Social history

- Level of education completed, occupation
- Marital status/number of children
- Handicapped? Disabled? Receiving social security benefits?

Note that many of the suggestions are redundant, a tactic that improves the likelihood of discovering useful information, even if the patient does not fully understand some of the questions

Table 1.2. Neuro-ophthalmic emergencies and their presenting symptoms

Emergency	Presenting signs and symptoms	Beware of:
Elevated intracranial pressure	• Papilledema (see Chaps. 8 and 12) • Bilateral sixth nerve palsies (see Chap. 10) • Acuity initially unaffected – later stages marked by transient visual obscurations • Parinaud's syndrome (see Chap. 11) • Headache (increasing in recumbency; see Chap. 16) • Vomiting while in a fasting state	• Brainstem compression • Cardiovascular or respiratory arrest • Hemorrhagic (retinal) infarcts in venous sinus thrombosis
Malignant hypertension	• Optic disc swelling consistent with papilledema, but accompanied by signs of systemic hypertension: • "Copper wiring" of arterioles • Arteriovenous crossing changes • Branch vessel occlusions • Hard and soft exudates • Visual acuity and general health initially unaffected	• Cerebral infarct • Myocardial infarct
Carotid dissection	• Acute Horner's syndrome (see Chap. 5) • Excruciating pain, radiating ipsilaterally into the neck, jaw, and/or ear • Spontaneous onset (predisposed in Marfan's or the Ehlers-Danlos syndromes) • After trauma (sports injuries or chiropractic manipulations)	• Embolic brain infarction
Pituitary apoplexy	• Hemianopic visual field defects (see Chaps. 3, 4, and 12) • Relative afferent pupillary defect (see Chap. 2) • Restricted ocular motility • Trigeminal nerve involvement (nerve V_{1+2}) • Optic atrophy in advanced stages of visual loss • In extreme cases, decrease in or loss of consciousness leading to coma	• Subarachnoid bleeding • Elevated intracranial pressure that is life threatening or potentially blinding
Cerebral infarct	• Signs of elevated intracranial pressure (see Chaps. 8 and 12) • Symptoms of hemiplegia or hemiparesis (see Chap. 21) • Ocular motility disturbances • Impairment or loss of consciousness	• Elevated intracranial pressure that is life threatening with loss of vital brain centers for respiration, thermoregulation and/or circulation
Aneurysms	• Acute oculomotor paralysis with pupillary involvement (see Chap. 10) • Abrupt and excruciating headache • Nuchal rigidity • Clouding or loss of consciousness (see Chap. 21)	• Subarachnoid hemorrhage
Multiple vascular occlusions	• Numerous retinal infarcts (cotton wool exudates) in the setting of a known or suspected endocarditis, paraneoplastic disorder, or vasculitis	• Cardiac arrest • Malignancies • Life-threatening cerebral infarcts
Wernicke's encephalopathy (thiamine deficiency)	• Nystagmus • Oculomotor deficits • Impaired consciousness • Other cranial nerve deficits • Alcoholic malnutrition • Parenteral administration of thiamine (vitamin B1) produces a rapid recovery	• Death by multiorgan failure
Orbital cellulitis	• Painful proptosis exophthalmos (see Chap. 9) • Restricted ocular motility • Inflammatory optic neuropathy (see Chaps. 8, 9 and 10) • Regional and systemic signs of inflammatory disease	• Septic cavernous sinus thrombosis (particularly dangerous: mucormycosis)
Giant cell arteritis	• Severe anterior ischemic optic neuropathy ([AION], see Chap. 8) • Pain and tenderness in the temples or scalp, aggravated when combing or brushing hair • Jaw claudication • Ocular motility deficits (rectus muscle ischemia) • Erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) markedly elevated • Anorexia • Malaise	• Blindness and/or life-threatening myocardial or cerebral infarction

Table 1.2. (*Continued*)

Emergency	Presenting signs and symptoms	Beware of:
Whipple's disease	• Rhythmic oculomasticatory movements are a pathognomonic disturbance of ocular motility: rhythmic convergence movements in synchrony with movements of the jaw and pharyngeal musculature • Cause: bacterial enteritis (Tropheryma Whippelii) • Clinical scenario: presents as a malabsorption syndrome	• Disease leads to death, when untreated, but curable with antifungal agent (clotrimazole)
Botulism	• Initially symptoms of a gastroenteritis (nausea, vomiting, constipation) starting 4 days after exposure (eating spoiled food) • Subsequent bilateral pupillary paresis with reduced light responses and complete paralysis of accommodation (see Chap. 5), eventually developing a complete external ophthalmoplegia • Further systemic paralysis, including the pharyngeal and respiratory muscles, and xerostomia	• Death by respiratory failure • Also wound botulism (puncture wound with deep anaerobic sepsis). Note: The entry wound may have already healed or may have been forgotten, making it difficult to find

Video 1.1

Chapter 2

Visual Loss of Uncertain Origin: Diagnostic Strategies

H. Wilhelm, U. Schiefer, and E. Zrenner

The practicing ophthalmologist faces a common challenge on a daily basis: A patient's vision is worse than was expected, based on the appearances of the initial examination. Usually, a renewed and more careful examination explains the discrepancy. Often, however, additional examination finds nothing to explain the conflicting findings. Time is limited, and one is tempted to refer the patient to a neurologist or another ophthalmic service. The diagnostic modalities available at the next site often lead to an unguided attempt at diagnosis when it is felt that some sort of explanation for the visual loss must be found. This scenario can be both expensive and dangerous, subjecting the patient to a random wandering through neurodiagnostic procedures. At the end of this process, the patient is unsatisfied and anxiety ridden and returns to the ophthalmologist or seeks the counsel of other physicians or even alternative medicine practitioners. If the ophthalmologist wishes to find the correct diagnosis by the most efficient means, he/she must analyze the clinical findings carefully before referring the patient, to arrive systematically and rationally at a conclusive, problem-oriented working diagnosis.

Diagnostic Strategy in Schematic Form

Pearl

An impairment of vision will have its source in one of the following categories: optical, macular, neural, chiasmal, or retrochiasmal visual pathway. There can also be an unrecognized developmental amblyopia, an open attempt at malingering, a functional or psychological disorder, or a simple exaggeration of the problem in an attempt to maximize a secondary gain (■ Fig. 2.1). For each of these categories, there are specific guidelines to the tests that will clarify the nature of the problem.

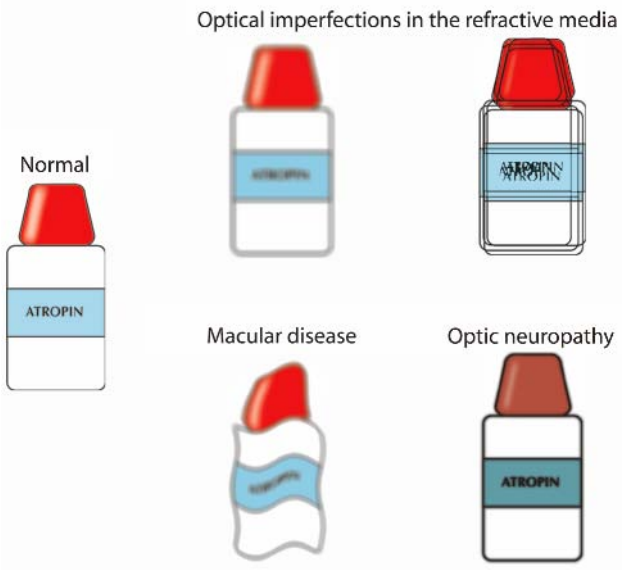
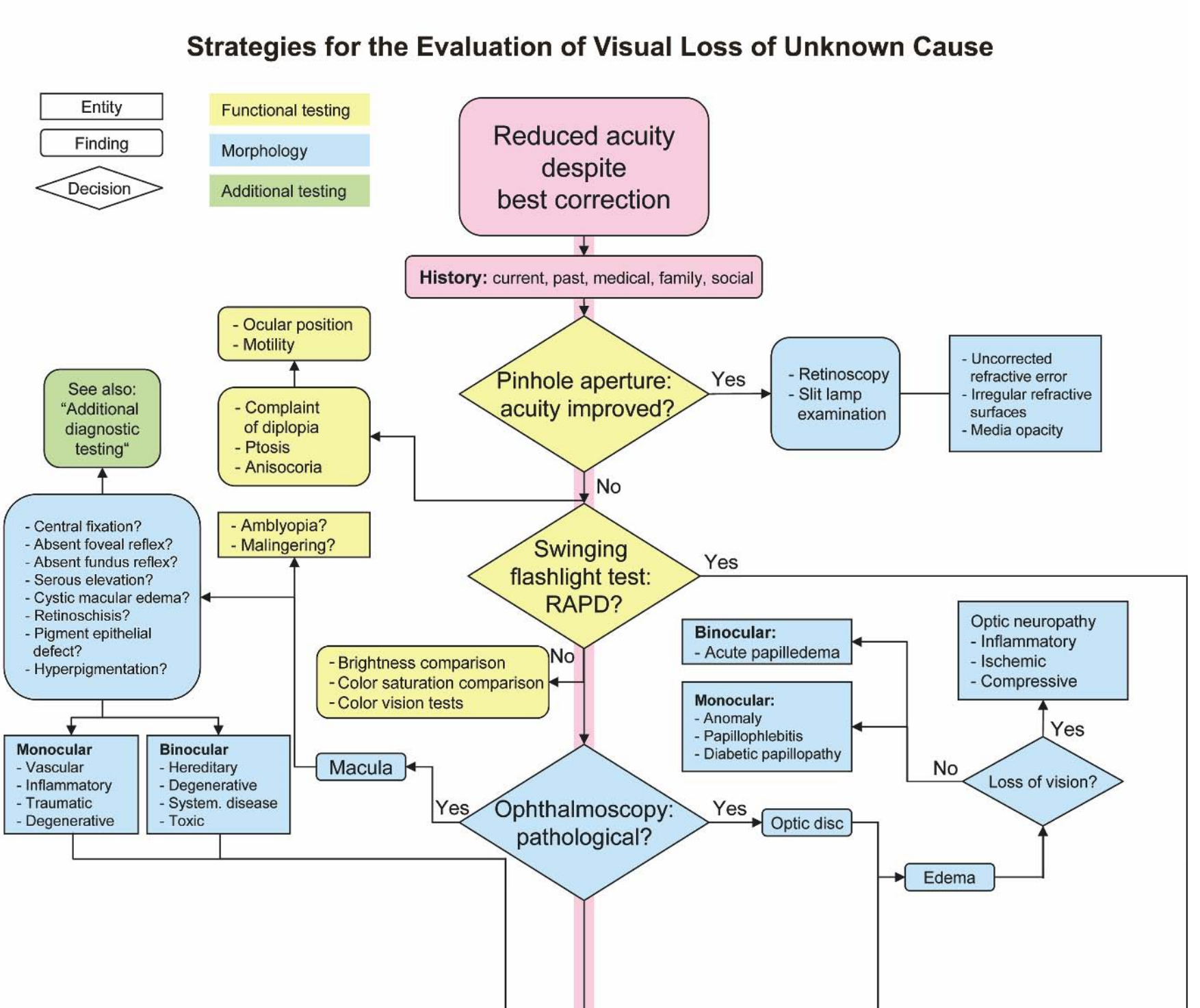
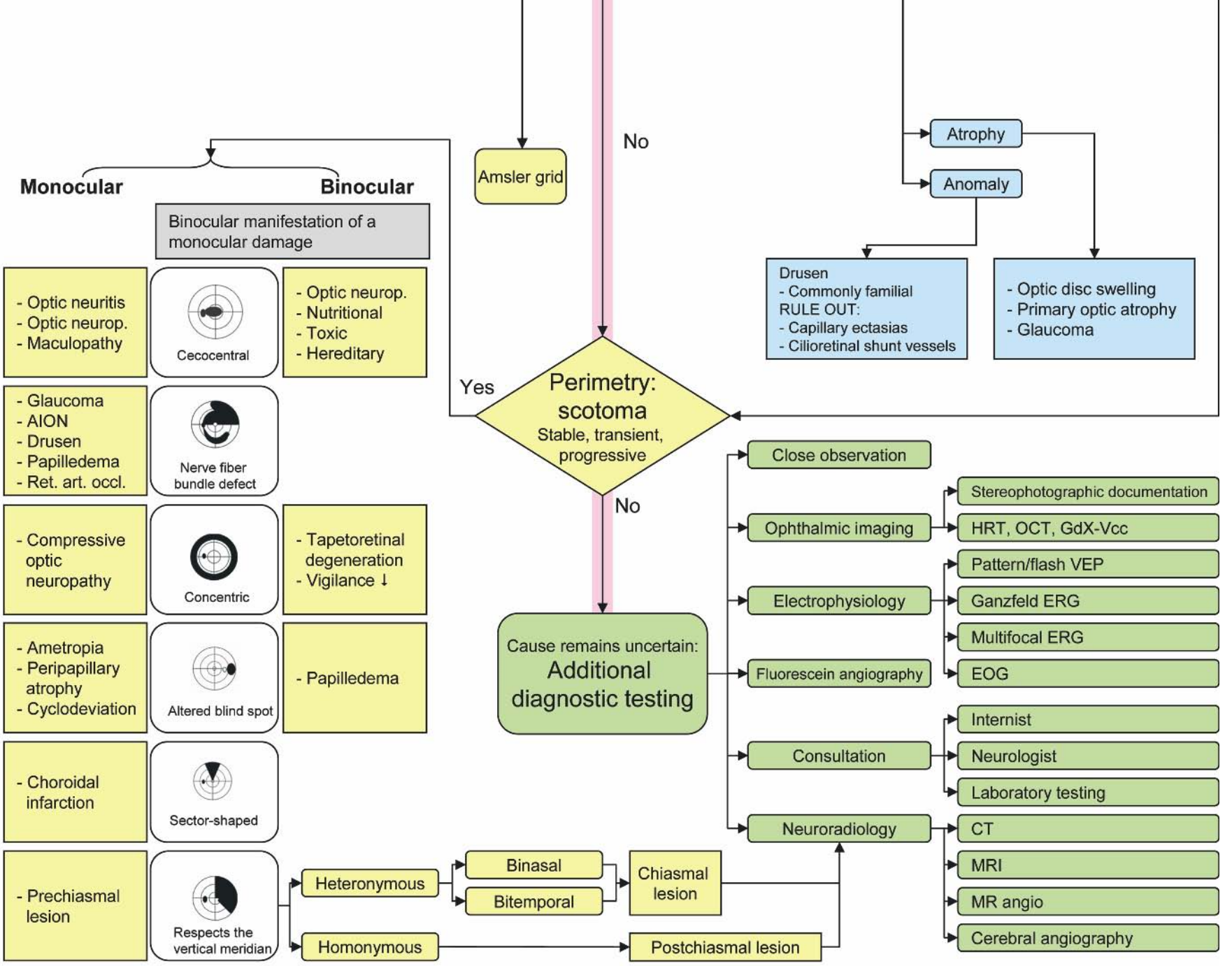


Fig. 2.1. How the patient characterizes his or her visual problem depends on the cause of the impairment. For refractive errors, the eye experiences blurring of images and double or ghosting of contrasting contours. The symptoms of macular disease are dominated by micropsia and metamorphopsia, whereas optic neuropathies more commonly are described as having darker images with poor color perception

Ruling Out Optical Causes of Reduced Vision

The first crucial datum is the corrected visual acuity. Problems are evident from the start, however, beginning with determination of the best possible correction. Despite the availability of automated refractometers, an experienced examiner can be led down the wrong path. What is more, there are optical problems that cannot be detected by conventional methods of clinical refraction.


Strategies for the Evaluation of Visual Loss of Unknown Cause
Entity
Finding
Decision
Functional testing
Morphology
Additional testing
Reduced acuity despite best correction
History: current, past, medical, family, social
Pinhole aperture: acuity improved?
Yes
- Retinoscopy
- Slit lamp examination
- Uncorrected refractive error
- Irregular refractive surfaces
- Media opacity
No
- Ocular position
- Motility
- Complaint of diplopia
- Ptosis
- Anisocoria
See also: "Additional diagnostic testing"
- Central fixation?
- Absent foveal reflex?
- Absent fundus reflex?
- Serous elevation?
- Cystic macular edema?
- Retinoschisis?
- Pigment epithelial defect?
- Hyperpigmentation?
- Amblyopia?
- Malingering?
Swinging flashlight test: RAPD?
Yes
No
- Brightness comparison
- Color saturation comparison
- Color vision tests
Binocular:
- Acute papilledema
Monocular:
- Anomaly
- Papillophlebitis
- Diabetic papillopathy
Optic neuropathy
- Inflammatory
- Ischemic
- Compressive
Yes
No
Loss of vision?
Monocular
- Vascular
- Inflammatory
- Traumatic
- Degenerative
Binocular
- Hereditary
- Degenerative
- System. disease
- Toxic
Macula
Yes
Ophthalmoscopy: pathological?
Yes
Optic disc
Edema



Flow diagram. Diagnostic strategies for the evaluation of visual loss of unknown cause

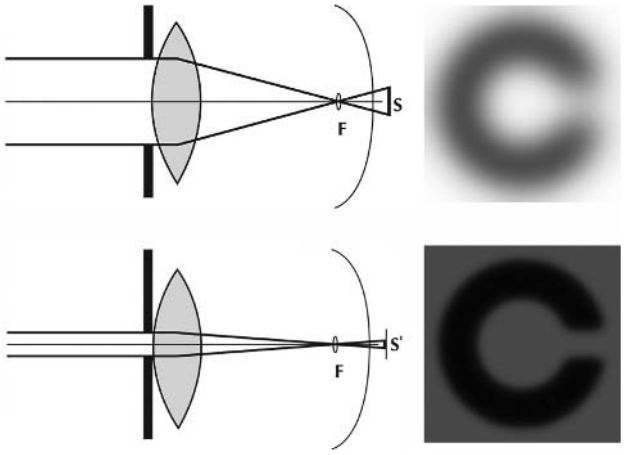


Fig. 2.2. The stenopeic slit minimizes the blur circle and enhances image focus in eyes with refractive errors

Use of the Pinhole Aperture, the Stenopeic Slit, and the Retinoscope

A simple stratagem is to provide the patient with a reduced aperture. The recommended type is a flat disc with several holes of about 1.5 to 2 mm in diameter, allowing the patient to locate the test characters quickly. Use of such reduced aperture devices will yield at least some improvement in spatial acuity in the presence of all possible (nonopaque) optical irregularities. Just as the diaphragm in a photographic camera allows control of the depth-of-field and permits both distant and near objects outside of the plane of focus to appear sharply defined, the artificial pupil serves as a stopped down diaphragm, giving the eye a focused image, despite optical imperfections (■ Fig. 2.2). All optical defects can be neutralized at least to some extent by this method, and not just the refractive ametropias. Irregularities in the corneal tear film, irregular corneal astigmatism (as with keratoconus), faults in the clarity of the lens, early cataract formation, and clouding of the posterior capsule after extracapsular cataract extraction are all frequent causes of unexplained reductions in acuity, which are easily missed or incorrectly dismissed as trivial.

Pearl

If the stenopeic slit or pinhole aperture results in an improvement of Snellen acuity by two lines or more, it is reasonably certain that an optical problem is playing a significant role in the patient's reduced vision.

To be sure, for most patients, improvement in visual acuity with the pinhole aperture is limited by the uncertainty of the method, so that an improvement of less than two lines must be viewed with some caution. Many patients find task of peering through the pinhole aperture difficult and cannot give a reliable response.

Note

For patients with visual disorders that cause photophobia, the light-reducing effect of the small aperture may be the factor responsible for visual improvement. If this is suspected, one should determine whether a neutral density filter has the same effect as the stenopeic aperture. If this is indeed the case, it suggests that the problem may be primarily retinal in origin.

Refractive errors can be verified objectively by retinoscopy. This simple test reveals disturbances of the refractive media very quickly, including subtle irregularities, and sometimes does so more effectively than the use of a slit lamp.

Visual acuity can also be measured objectively with laser interference instruments. However, this method is not always available, and in cases of amblyopia can produce an unrealistic overestimate of the true acuity.

Note

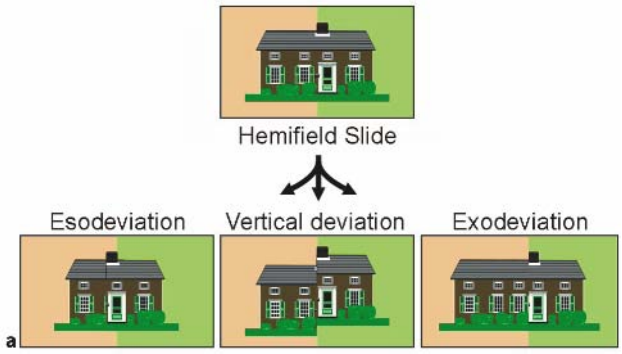
Patients with pituitary adenomas, chiasmal compression, and bitemporal hemianopias usually do not report a sensation like that of wearing horse blinders, because the function of each blind temporal hemifield is taken over by the nasal hemifield of the contralateral eye. Instead, they often report (with some difficulty) an unusual deficit in their vision, variously described as doubling of images or problems with reading. What they are noticing is the loss of all binocular vision. Each hemifield is seen by one eye only, thus removing the sensory basis for binocularity. This completely neutralizes the normal fusional vergence reflex that maintains ocular alignment, producing nasal visual hemifields that variously overlap (in those with esodeviations), separate (in those with exodeviations), or shift vertically (in those with hyperdeviations). This is often referred to as the hemifield slide phenomenon (■ Fig. 2.3a).

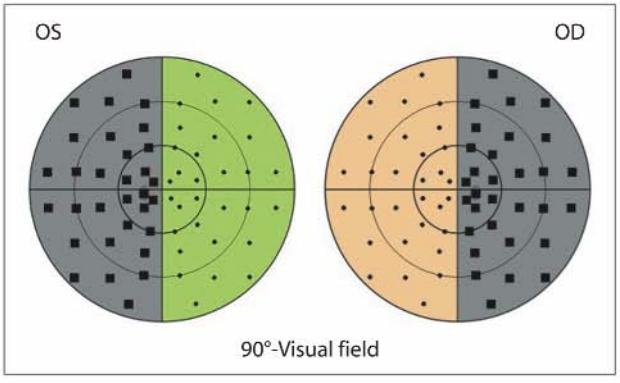
Animation 2.1

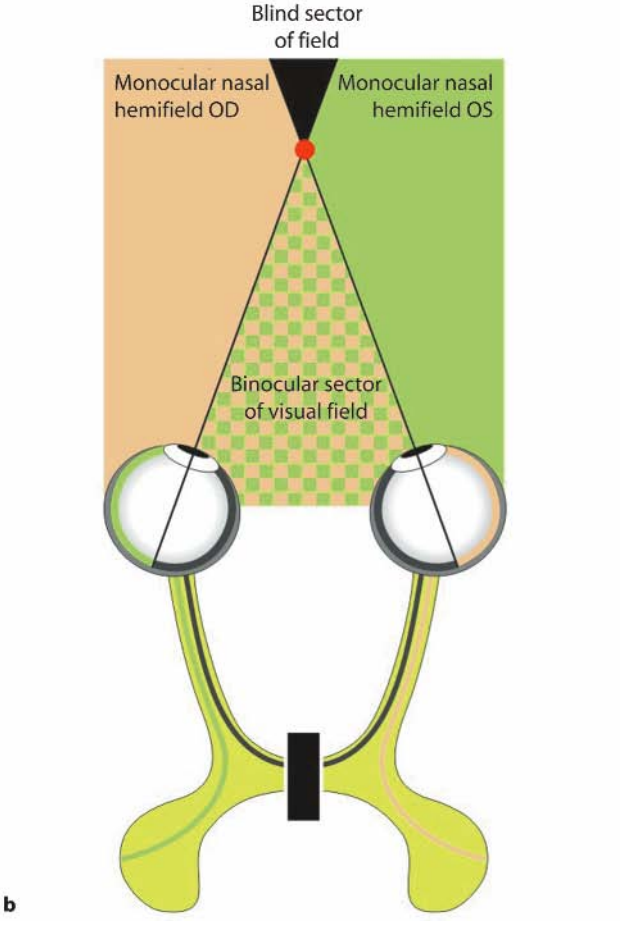
Another consequence of a complete bitemporal hemianopia is referred to as postfixational blindness. When both eyes fix on some object of regard, there is a triangular area of blindness, located with its apex at the point of regard and widening beyond that point, hence the term postfixational. This phenomenon results from loss of that portion of the visual field needed to see objects that are directly in the line of sight, but which are positioned beyond the object of regard (■ Fig. 2.3b).

Fig. 2.3. **a** The hemifield slide phenomenon in a case of complete bitemporal hemianopia, and its effect on object perception. **b** The effect of a complete bitemporal hemianopia when fixing on nearby objects: Objects beyond the point of fixation (*red*) disappear completely

Animation 2.2







Animation 2.3

When an Optical Disturbance Is Found

If the Snellen acuity can be improved by a reduced aperture device or if there are visible irregularities in the media (often best seen in the reflected light of the fundus reflex through a dilated pupil), there should be a systematic search for any or all of the following causes.

Incorrect Refraction

A repetition of the subjective and objective refractions with pupillary dilation and cycloplegia is necessary. This will occasionally uncover an undetected or an irregular corneal astigmatism.

Corneal Disorders

Corneal epithelial disease can cause profound losses of visual acuity. The most common cause of this problem is a defective tear film. Not uncommonly, patients with follicular conjunctivitis are referred to the ophthalmologist. Their symptoms, blurring and ocular pain that is sometimes aggravated by ocular movement, can falsely suggest the possibility of optic neuritis. This mistake can be corrected by everting the upper lid, exposing the (sometimes giant) follicles. In addition, the visual problems caused by marginal blepharitis and/or chalazions are frequently underestimated, though they can produce significant changes in corneal astigmatism with associated reductions in acuity.

Since the corneal surface is the strongest refracting interface of the eye, seemingly insignificant disturbances, such as off-axis corneal scars, dystrophies, or a roughened tear film, will sometimes have a profound effect on the Snellen acuity. Early keratoconus is easy to miss, and it is often first discovered in adults with established histories of unexplained vision problems. Ophthalmometry, retinoscopy, and use of the Placido disc for corneal topography scanning are often necessary to establish the diagnosis. In this instance, a rigid contact lens on the cornea will markedly improve the image clarity and confirm the refractive nature of the poor acuity.

Lenticular Disorders

Cataracts are rarely missed. Nevertheless, subtle loss of lens clarity, early haziness, clefts, posterior subcapsular densities, and irregular refractive interfaces in nuclear sclerotic lenses can be difficult to see at the slit lamp. Occasionally, the problem is discovered only after repeated examinations. A contact lens will not improve the acuity, although a reduced aperture (pinhole disc) usually will. The problems are aggravated by decreasing illumination and/or increasing pupillary size. Rather typical for this problem is the complaint of monocular diplopia, shadowing, or ghost

images that parallel clearly defined contours of high contrast within images. Occasionally, patients with this problem are referred to the strabismus surgeon when the complaint of diplopia is mistaken for a binocular problem. The ghosting of images caused by faults in lens clarity will invariably improve with the pinhole aperture disc.

Swinging Flashlight Test

If an optical defect has been ruled out, the swinging flashlight test is the next step in defining the nature of the problem. It is used specifically to detect evidence of an (asymmetric) optic neuropathy.

Video 2.1

The test is conducted as follows (■ Fig. 2.4). The patient is asked to fixate on a distant object in a dark room. An indirect ophthalmoscope or a halogen bulb flashlight can serve as the light source. One should illuminate the eyes with the light source held below the level of the line of sight, elevated at about a 45° angle (so that the patient can see over and beyond the light source). Initially both eyes are illuminated from two separate distances, during which one should note whether the two pupils are equal in size and whether they respond well to the light (see Chap. 5). If no anisocoria is found and the pupils respond well to the light stimulus, the test can begin.

Video 2.2

Using a somewhat dimmer light, one eye is illuminated, and after 2 to 3 s, the light is shifted quickly to the contralateral eye. After another 2 to 3 s, the light is shifted back to the original eye. Since the pupillary responses can vary significantly, the process is repeated four or five times. During this alternation of monocular light stimuli, the following events take place. As the first eye is illuminated, its pupil constricts and stays small until the light is shifted to the contralateral eye. During the transfer, both pupils dilate somewhat. The more slowly one shifts the light, the greater the extent of bilateral dilation. In fact, 2 or 3 s is sufficient time for the level of retinal light adaptation to change: The unstimulated eye dark adapts to a small extent. For this reason, both pupils constrict again when the light arrives at the contralateral eye. The unstimulated eye dark adapts again, and the cycle begins anew. The examiner closely observes the speed and extent of the pupillary constriction in the newly illuminated eye and compares the results seen in each side. If one pupil consistently constricts more weakly than does its partner, the examiner has uncovered manifest evidence of pathology. If the initial constriction is weaker, or if the pupil actually dilates on arrival of the light stimulus (so-called pupillary escape), there is a relative afferent pupillary defect, and the examiner can be certain of an optic neuropathy.

Video 2.3

Video 2.4

It helps to remember that the crux of the test lies in a comparison of the pupils' consensual responses and their corresponding direct responses. If the consensual response is consistently and clearly better than the direct response, the ipsilateral optic nerve has a relative deficit, whereas if the direct response is consistently and clearly better than the consensual response, the contralateral optic nerve has a relative deficit.

Relative Afferent Pupillary Defect

Definition

If the swinging flashlight test detects an abnormality, one can conclude that there is a **relative afferent pupillary defect (RAPD)**. It is said to be relative, since the defect is always detected by comparison of one eye to the other.

The examiner must observe the patient rather closely during this test, since the pupillary light reactions can vary considerably. When the pupils react sluggishly, a slower transfer will allow better dilation and greater constriction on arrival at the contralateral eye. For briskly reactive pupils, on the other hand, a quicker transfer of the stimulus is more helpful. In addition, the brightness of the light and its distance from the eye can affect the extent of constriction. With a too strong (or bright) stimulus a subtle RAPD might be overlooked because the pupillary sphincter will always reach its maximally constricted size independent from the state of the afferent system.

Note

The test is simple, but care must be taken to avoid the following sources of error:

- Variations in the distance and angle of illumination (of one eye relative to the other)
- Variations in the time spent observing one eye, relative to the other
- A stimulus that is either too bright or too dim
- Changes in the patient's fixation or accommodation during the test

The test cannot be used validly if one or both pupils do not react to light, or if there is a significant anisocoria. However, since both pupils normally react synchronously, it is usually enough to focus attention on the better reacting pupil while comparing its direct to its consensual light reactions. To allow observation of the pupils in the darkened examination room, the examiner can illuminate the eye(s) tangentially from one side in a plane that is parallel to that of the pupil. Using a separate light source, one can then

Video 2.5

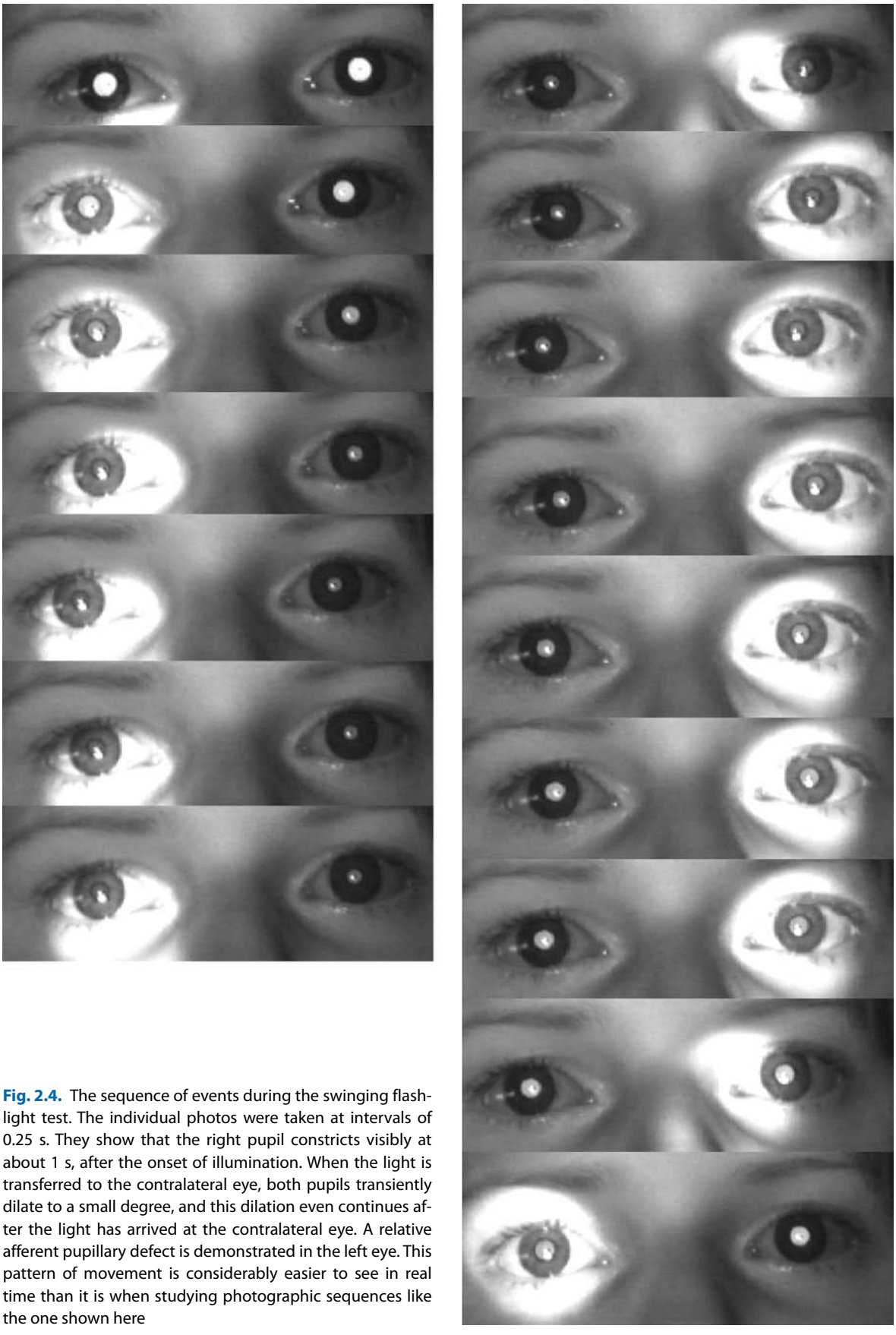


Fig. 2.4. The sequence of events during the swinging flashlight test. The individual photos were taken at intervals of 0.25 s. They show that the right pupil constricts visibly at about 1 s, after the onset of illumination. When the light is transferred to the contralateral eye, both pupils transiently dilate to a small degree, and this dilation even continues after the light has arrived at the contralateral eye. A relative afferent pupillary defect is demonstrated in the left eye. This pattern of movement is considerably easier to see in real time than it is when studying photographic sequences like the one shown here

perform the alternating test. If the direct response is better than the consensual, there is a relative afferent pupillary defect in the contralateral eye, whereas if the consensual response is better than the direct, the defect is in the ipsilateral eye.

If both pupils react very poorly to light, the test cannot be used.

Pearl

If one is not certain whether there is an RAPD, it helps to repeat the swinging flashlight test with the use of neutral density filters. A weak filter with 30 to 40% absorption is held before one eye or the other while carrying out several repetitions of the test. If there is no RAPD, the artificially created afferent defect will be present in the eye with the filter in place, and will migrate to the opposite eye when the filter is transferred. This use of a filter sometimes fails to clarify the problem, but if there really is an RAPD, it will be significantly enhanced when the filter is held before the affected eye.

When examining infants or small children, the test can be done with the use of a direct ophthalmoscope. The examiner observes the fundus reflex from a distance of arm's length or greater, where the child is more likely to feel less threatened.

The presence of an RAPD cannot rule out the presence of an optic neuropathy in the contralateral eye. It is possible (and not uncommon with some diseases) for there to be bilateral optic nerve damage that is simply greater in one eye than in the other. Conversely, if both optic nerves are damaged to the same extent (no matter how severe it might be), there will be no detectable RAPD.

The crucial importance of the swinging flashlight test is apparent when one considers the many disorders in which an RAPD can develop (■ Table 2.1).

Table 2.1. The relative afferent pupillary defect (RAPD) and the differential diagnosis of the sign

The source of the visual loss	An RAPD is found . . .:
Optical defect in the refractive media of the eye	Never (with the sole exception of a very dense vitreal hemorrhage)
Macular disease	Only when the visual damage is strongly asymmetrical and very severe
Unilateral optic neuropathy	Always
Bilateral optic neuropathy	Only when asymmetrical
Chiasmal disease	Frequently
Optic tract disease	Nearly always (contralateral to the affected tract); remember that the contralateral temporal hemifield is larger that the ipsilateral nasal field
Retrogeniculate disease	Sometimes (contralateral to the affected side, and usually in developmental anomalies of a cerebral hemisphere associated with transsynaptic degeneration at the lateral geniculate body)
Amblyopia	Rare (usually subtle defects that are most often associated with unilateral optic nerve or macular hypoplasia)
Psychogenic unilateral visual loss	Never
Marked anisocoria	Minor (on the side with the smaller pupil)
Uncovering of the eye (bandage, lid)	Transient (contralateral, caused by differing levels of dark adaptation that quickly equilibrate)

Video 2.7

Video 2.6

Note

A disturbance of the optical media, including acuity reduction to the level of light perception, can (almost) never cause an RAPD in the affected eye. This surprising fact is explained by the scattering of light in eyes with cloudy media, causing indirect stimulation of the foveal macula, which has high pupillomotor sensitivity. If the lens of the eye is clear, the stimulus light will fall largely on the less sensitive portions of the peripheral visual field, illuminating the interior of the eye diffusely but after significant absorption of the light by the pigment epithelium of the retina and the melanocytes of the choroid. It is even possible for an eye with a clouding of the media to have a stronger pupillary light reaction. A monocular or asymmetric optic neuropathy, on the other had, will always produce an RAPD as a result.

Pearl

Using neutral density filters or varying transmission, one can quantify an RAPD by weakening the light stimulus as it is presented to the better eye. The density of a filter that neutralizes the RAPD provides a measure of the deficit. The filters found to be useful for this method are separated in 0.3-log unit steps from 0.3 to about 2.0 log units. The strength of an RAPD correlates with the extent of visual field loss, when comparing one eye to the other, especially when the cause is a compression of the optic nerve.

Video 2.8

When no filters are available, one can substitute a variation in the distance between stimulus and eye: Doubling the distance weakens the stimulus by about 0.6 log units. One can occasionally encounter unusual instances of a subtle RAPD in a healthy eye, but never one as large as 0.6 log units. Quantification of an RAPD is important in three specific situations:

1. As an additional objective measure of the course of optic neuropathies, especially when perimetry is not usable
2. When amblyopia is suspected as the cause of a visual deficit, an RAPD of 0.6 log units or more is very unusual and must initiate a critical reappraisal of the diagnosis. (An RAPD can be found in an amblyopic eye that has an identifiable developmental hypoplasia of the retina and/or optic nerve.)
3. In eyes with a central retinal vein occlusion, an RAPD of 0.9 log units or more is a reliable sign of the ischemic form of the disease, and alerts the physician to the risk of neovascularization

Brightness and Color Comparison Tests

The information obtained with the objective swinging flashlight test can be expanded with subjective tests. Thus, an eye with an optic neuropathy will see a light as less bright than will its unaffected, contralateral partner. Colors are, by similar comparison, seen as faded (desaturated) or darker than in the healthy eye. This test is easily done with the use of a small, colored object that is shown to one eye and then to the other (the red cap from a mydriatic bottle suffices). Patients with macular diseases see a light as brighter and colors – at least initially – as normal. The most important symptoms of macular disease are metamorphopsia and micropsia.

! Note

Color and brightness comparisons are subjective tests. The results are not always precise, and false positive responses are not uncommon. Very observant patients can accurately identify small differences in color or luminance perception caused by differing levels of retinal light adaptation. The uneven illumination of a desk lamp will commonly produce a higher level of light adaptation in the eye closer to the light, while the contralateral eye lies in the shade cast by the nose. While they are helpful as confirmation tests, these subjective comparisons are not at all as valuable as the swinging flashlight test, and cannot be substituted for the objective form of testing.

When a Relative Afferent Pupillary Defect Is Demonstrable

If the swinging flashlight test clearly demonstrates the presence of an RAPD, the next step in clinical analysis of the vision loss is testing of the visual field. The first priority is detection of an optic neuropathy, or an asymmetric chiasmal or optic tract lesion. For this purpose, perimetry is necessary. A detailed account of this testing can be found in Chaps. 4 and 8.

When no relative afferent pupillary defect is demonstrable, a bilateral, symmetrical optic neuropathy, a lesion of the chiasm, or a retrochiasmal lesion must be ruled out. Perimetry helps in this case also.

Perimetry

Perimetry is the primary testing modality for the detection of chiasmal and retrochiasmal disorders. The goal is to define the shape and extent of the visual field loss, which in turn provides decisive clues to the kind and location of responsible lesions (see Chaps. 3 and 4). Neuro-ophthalmology is not primarily concerned with measuring an index of the visual field's collective sensitivity or with statistical analysis for differentiating localized from more general forms of visual field loss. Rather, it is primarily concerned with the configuration or spatial pattern of the visual damage.

Perimetry is so important to neuro-ophthalmology that a separate chapter in this book has been devoted to the subject (Chap. 4). It determines not only whether diagnostic imaging is needed, but actually provides focally diagnostic clues and can help the radiologist by providing an indication of where the disease is most likely to be found. When perimetry and the appearance of the optic disc do not clarify the source of the problem, it is most likely that a maculopathy is at fault.

Search for a Macular Disorder

There are retinal disorders that produce a change neither in the ophthalmoscopic nor in the biomicroscopic appearance of the retina that would indicate the presence of a disease. In addition, many significant fundus signs can be very subtle. Most frequently, macular edema is overlooked. Its characteristic symptom is not so frequently metamorphopsia, but rather micropsia (■ Fig. 2.5). This is so typical that an observant patient could provide the decisive diagnostic clue in a telephone conversation. Haploscopic image separation by polarizing or colored filters is helpful, and even

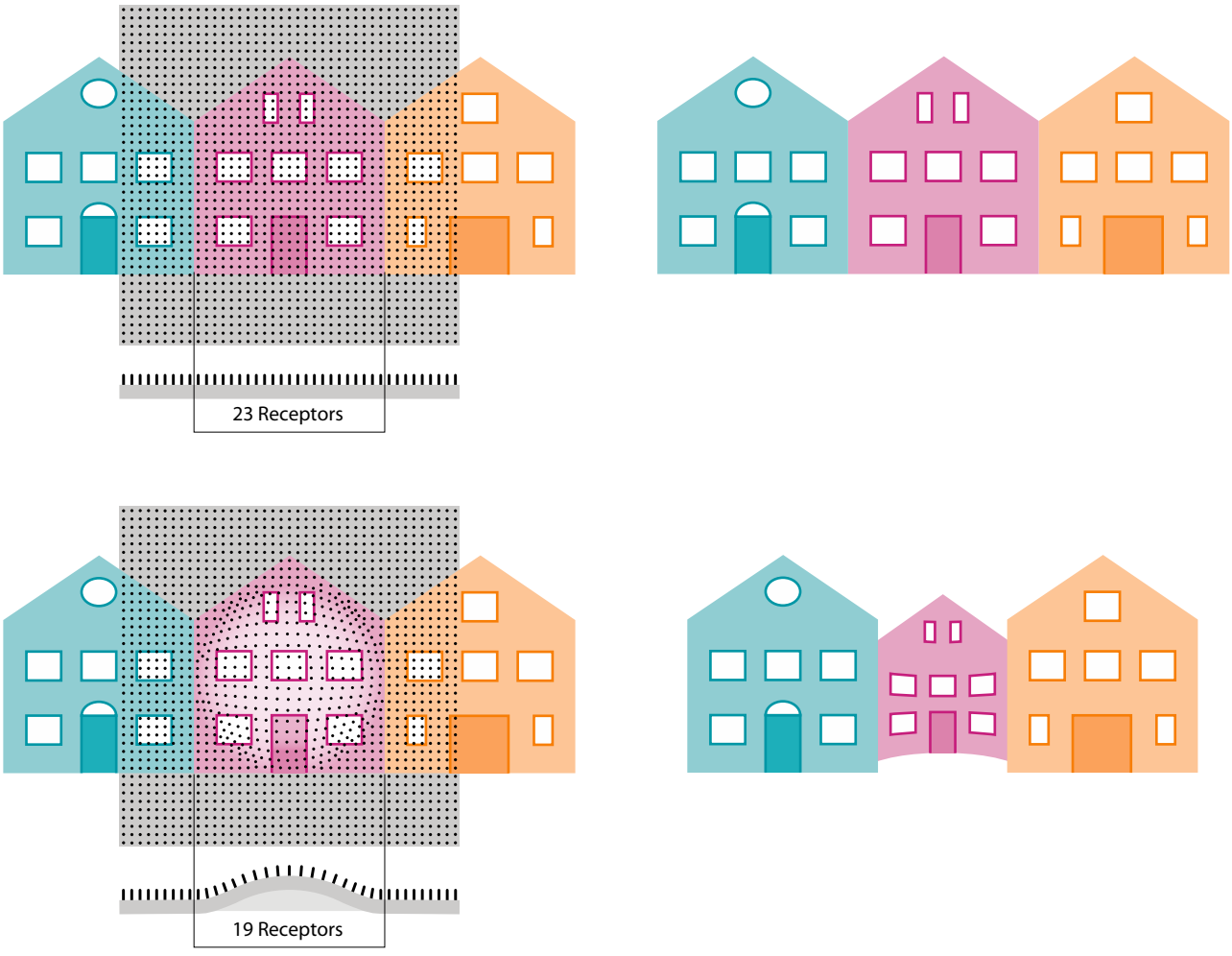


Fig. 2.5. The basis of micropsia in cases of macular edema: The photoreceptors are spread from one another, and the retinal image falls on a smaller group of receptors

simple alternating cover/uncover testing is sufficient. The diagnosis can be established objectively by optical coherence tomography (OCT) or by fluorescein angiography. Macular edema also produces a characteristic change in the visual field, allowing one to confirm the diagnosis even when the ophthalmoscopic appearance is hidden, e.g., by a small, rigid pupillary aperture. In this situation, one needs to use threshold static perimetry, which will demonstrate the presence of a relative central scotoma.

There are a number of disorders of the photoreceptors, the pigment epithelium, or the retinal neuronal circuitry in which the damage to vision is much more severe than one would expect based on the fundus appearance alone. In particular, hereditary and toxic disorders easily elude diagnostic detection. A well-done history taking is usually decisive. Photophobia and hue discrimination deficits suggest a problem with cone function, poor scotopic vision with rod function. One should note also that the problems of nyctalopia must be specifically asked about. The statement "My night vision is very bad" is much too sweeping and is often spontaneously offered. As a rule, patients are only describing an awareness of physiological changes in vision with nocturnal dark adaptation. In other cases, there is poor refraction or dry eye, which, when combined with a large pupil, results in a blurred retinal image.

Pearl

The patient with true nyctalopia, when asked "How easy is it for you to go for a walk outside on a moonless night?" will often reply "I would need to have someone lead me."

Instruments like the mesoptometer and nyctometer test mesopic vision, i.e., a combined function of both rods and cones. These devices are not suited to the proper testing for evidence of nyctalopia. Patients with retinitis

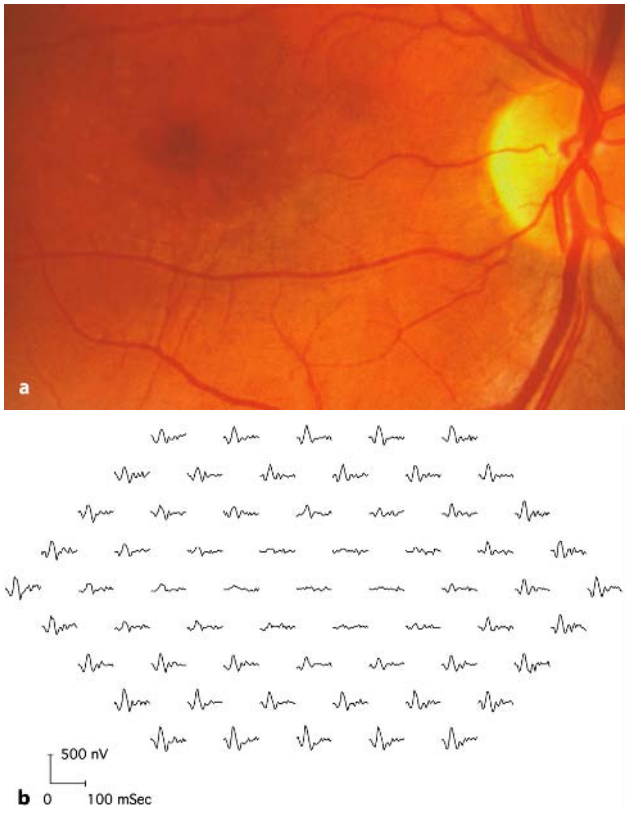


Fig. 2.6. **a** Stargardt's disease. The fundus is initially completely normal in appearance. **b** Multifocal electroretinogram (ERG) study shows the central defect. In this method, a local ERG is calculated for each retinal locus (see Chap. 7). In this manner, an electrophysiological campimetry of the central visual field is produced. In the study illustrated here, covering the central 30° of the visual field, normal ERG responses are seen in the peripheral loci of the examination, whereas in the center of the field they are either strongly reduced or completely lost

pigmentosa and pronounced nyctalopia can respond well when tested with these instruments. Conversely, uncorrected myopia can cause severe problems with vision at twilight, even when dark adaptation testing indicates normal function.

Further diagnostic testing for macular disease usually depends on the examiner's initial suspicion. In cases of cone disease, color discrimination tests help (see Chap. 6) to narrow the search more closely or even allow a confident diagnosis. If there is a disease of rods, on the other hand, dark adaptation testing is more helpful. A Ganzfeld electroretinogram (ERG) is likely to be helpful in both instances, since it includes both scotopic and photopic test conditions, providing objective and independent measures of rod and cone function (see Chap. 7). Still, there must be widespread damage to receptors to produce a clearly abnormal ERG. Local defects in foveal cones, such as in Stargardt's disease, can cause a substantial reduction without affecting the Ganzfeld ERG. This problem has recently been solved with the use of the multifocal ERG, which when used with Sutter's m-sequence technique has revolutionized clinical electrophysiology of the retina (■ Fig. 2.6; see Chap. 7). With this method, one can produce a map of electroretinographic responses in which very small central or paracentral lesions are revealed. Testing for Stargardt's disease is a perfect example.

Recommended tests of color vision are the desaturated panel D-15 test and the use of anomaloscopy. The Ishihara plates are more suited to the screening for hereditary red–green dyschromatopsias. Anomaloscopes are not widely available, but are in use at a number of university medical centers and schools of optometry in North America. In addition to the diagnosis of classical dyschromatopsias, this instrument can demonstrate so-called scotopization, which is typical for Stargardt's disease as well as for heredofamilial achromatopsia.

In the differential diagnosis of retinal disorders, one should keep in mind that nearly all hereditary and toxic retinopathies are bilateral and are usually symmetrical. Fluorescein angiography, electrophysiology, family pedigrees with familial testing, and additional evaluation by an occupational medicine service, when indicated, can all contribute to a confident identification of the correct diagnosis of primary retinal disorders. Electrooculography (EOG) testing is of value specifically for diseases of the retinal pigment epithelium, e.g., for Best's vitelliform degeneration.

A steadily increasing portion of heredofamilial diseases that affect vision can be detected with the methods of molecular genetics (see Chap. 18).

When diagnosing macular disease, one encounters a number of limitations (■ Table 2.2). Choroidal ischemia, smaller retinal infarcts, and incompletely expressed forms of a variety of disorders (as well as by carriers of recessive traits) create many obstacles for the diagnostician. An example is those patients with modestly reduced acuity, a blond fundus, and a granular appearance to the macular pigmentation. Transillumination shows incomplete pigmentation of the iris, and all such patients have had nearly white hair during childhood. This is the typical clinical presentation of an abortive form of ocular albinism in which the usually associated nystagmus is absent.

For most of these disorders, there are no effective treatments, but arriving at a correct diagnosis is nonetheless important, since this will allow for a clear indication of the prognosis for future visual function, which in turn permits planning of social aspects of life, educational opportunities, and rehabilitation services. Finally yet importantly, the physician must be able to confidently differentiate between primary retinopathies and optic neuropathies.

Table 2.2. Examples of easily missed retinal disorders

Disorder	Decisive tests
Macular edema of various sources	Fluorescence angiography, perimetry, optical coherence tomography (OCT)
Early stage of Stargardt's disease	Multifocal electroretinogram (mf ERG)
Juvenile retinoschisis	ERG, family history of ocular disorders
Ocular albinism	Iris signs, VEP (asymmetric decussation at the optic chiasm)
Cone dystrophy	Ganzfeld ERG
Achromatopsia	Ganzfeld ERG
Retinitis pigmentosa sine pigmento	Ganzfeld ERG and molecular genetic tests where indicated
Toxic retinopathies	Ganzfeld ERG/electrooculogram (EOG)
Choroidal infarction	Multifocal ERG (mfERG)/ indocyanine green angiography
Carcinoma or melanoma-associated retinopathy	Ganzfeld ERG
Unusual macular disorders, such as pattern dystrophy, acute zonal occult outer retinopathy (AZOOR)	If indicated, mfERG

Table 2.3. Amblyopia

Pros	Cons
"That eye has always had poor vision"	Good stereoacuity
Patching of an eye during childhood	RAPD
Monocular strabismus	Alternating fixation
Significant anisometropia	Difference of less than 2 D
High hyperopia	Hyperopia of less than 3 D
High astigmatism	Astigmatism of less than 2 D
Crowding phenomenon	Dominant eye poorer
Eccentric fixation	Steady central fixation
Ammann test: no further deterioration of acuity when viewing the chart through a neutral density filter (an amblyopic eye behaves as if it is already dark-adapted)	Pathological Ammann test, i.e., there is further deterioration of acuity when viewing the chart through a neutral density filter

D Diopters

Pearl

Micropsia suggests macular edema; color tests and dark adaptation testing help with identifying primary retinal disorders. With anomaloscopy, one can buttress the validity of a diagnosis of Stargardt's disease or heredofamilial achromatopsia. The ERG is the court of final appeal for atypical cases of primary retinal diseases, but also fails to detect focal lesions, for which the multifocal ERG is needed. Family history, occupational history, and queries with regard to exposure to toxic substances are all important. Genetic analysis permits the early identification of a number of heredofamilial disorders of vision, and the EOG helps to identify primary pigment epithelial diseases.

Diagnosing Amblyopia

The diagnosis of amblyopia requires that there is no optic atrophy or maculopathy and there is no high-grade RAPD (defined as 0.6 log units when measured by neutral density filters). Typically, the patient will report that the vision in the eye has been poor since early childhood. Frequently, the patient with an injury or an episode of inflammatory activity plausibly associates the cause of the poor vision. In all likelihood, the event was only a cause for drawing attention to the eye and discovery of its poor acuity. Not uncommonly, the history given by the patient and the patient's family can be useless. Some patients even forget that they have had strabismus surgery. Patient questioning and verification of the information (when possible) is needed.

Note

If the Lang stereotest finds evidence of good stereopsis, one can rule out strabismic amblyopia and/or microstrabismus (even though occasional exceptions are found). Bilateral amblyopia must have a convincing cause: very high hyperopia, high corneal astigmatism, ocular malformations. A myopic eye (or the more myopic of a pair) only rarely develops a refractive amblyopia if the refractive error is not extreme. A dominant eye cannot be amblyopic relative to its nondominant partner (■ Table 2.3).

Further options for diagnosis of an amblyopia include the Ammann test, tests of the crowding phenomenon, and acuity when reading. In the Ammann test, there will be no further reduction in acuity when a neutral density filter is held before the amblyopic eye – the amblyopic eye behaves as if it were already dark-adapted. The crowding phenomenon compares legibility of single characters as opposed to rows of characters. The mode of fixation can (but should not) show evidence of eccentric fixation. A profound or

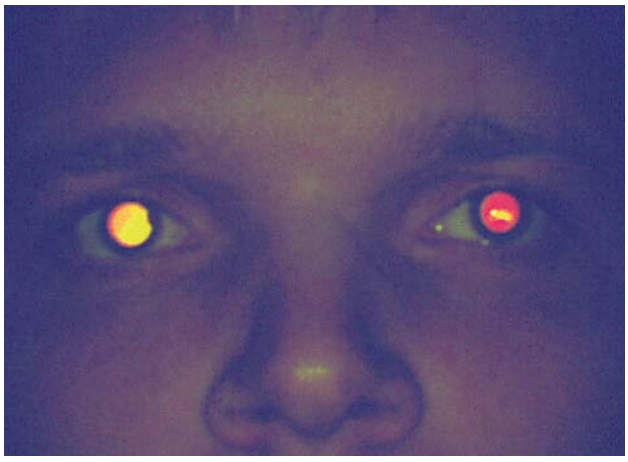


Fig. 2.7. The Brückner test: An interocular difference in the fundus reflexes is seen, signaling the presence of a problem. The possible sources include strabismic malalignment, a defect in the refractive media, or an interocular difference in fundus color (e.g., with high axial myopia or a fundus coloboma)

absolute central scotoma would exclude amblyopia as the principal cause of visual impairment, and would more commonly be the cause of eccentric fixation.

A quick and very helpful test of strabismic diagnosis is the Brückner test, in which one compares the fundus reflexes from both eyes (■ Fig. 2.7). The nonfixing, strabismic eye will have a brighter fundus reflex than its partner. However, a secondary strabismus because of damage to the visual system will also yield a positive Brückner test.

In short, one must use a number of measures for the diagnosis of amblyopia when the history is not clear.

Pearl

There is no reliable test to prove or exclude amblyopia. There are, however, numerous tests whose results can make the possibility of amblyopia so improbable that one cannot consider amblyopia as a plausible source of an unexplained visual deficit. The examiner should never be satisfied with a single test, and in cases of doubt should be very reluctant to accept amblyopia as a cause.

Malingering

Simulation of visual loss plays a significant role among the patients attending any ophthalmic clinic, and is probably undetected in a number of cases. A separate chapter has been devoted to this subject (see Chap. 15).

Conclusion

The strategy outlined here should allow the examiner to classify quickly the source of the problem. No single method is certain to be effective. Any objective test can be conducted or interpreted incorrectly. Simply the combination of several different tests and proper attention to the logical context of the case help to ward off a mistaken diagnosis. Of course, a carefully taken history and a thorough ophthalmologic examination are necessary for correct interpretation of the patient's problem. Not uncommonly, successful analysis of visual loss of an uncertain nature will require the cooperation of several specialty fields. Nonetheless, the ophthalmologist must take part from the very start in the full spectrum of diagnostic studies needed to make a correct diagnosis.

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Chapter 3

Functional Anatomy of the Human Visual Pathway

U. Schiefer and W. Hart

Nearly a half of all cortical neurons are devoted to the processing of visual information. The afferent visual pathway from the retina to the primary visual cortex has four neuronal elements (■ Fig. 3.1).

- First neuron: photoreceptors
- Second neuron: bipolar cells
- Third neuron: retinal ganglion cells (and their axonal processes, including the chiasm and optic tracts)
- Fourth neuron: geniculocalcarine neurons

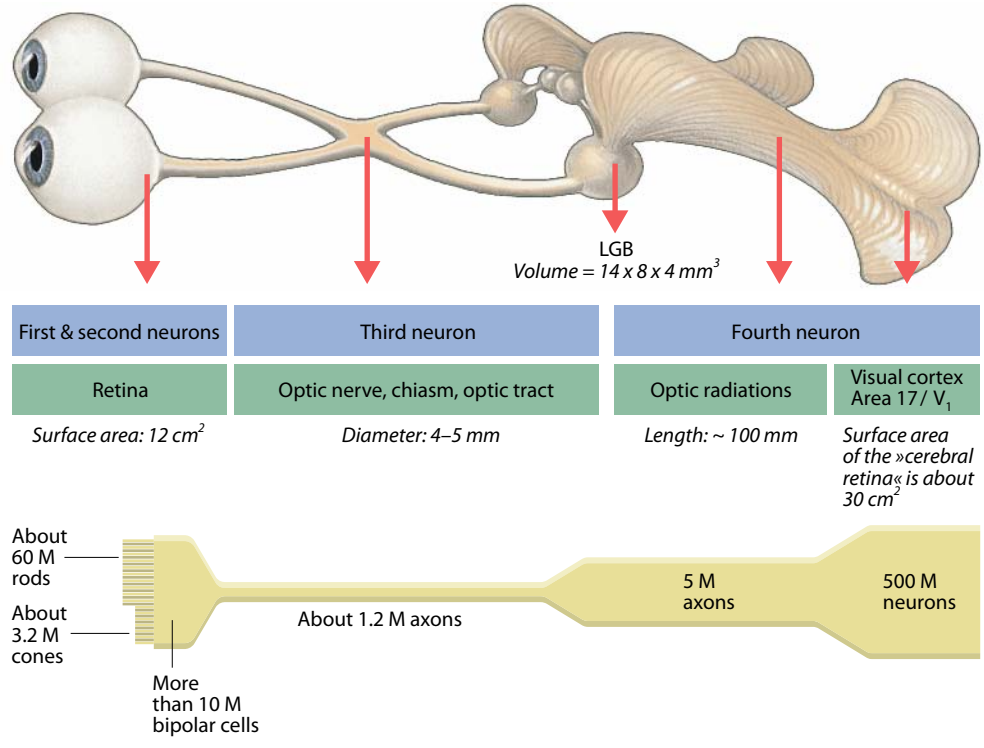


Fig. 3.1. Schematic diagram of the human visual pathways and their neuronal components. *LGB* Lateral geniculate body (modified after Krey et al. 1986; see "Further Reading")

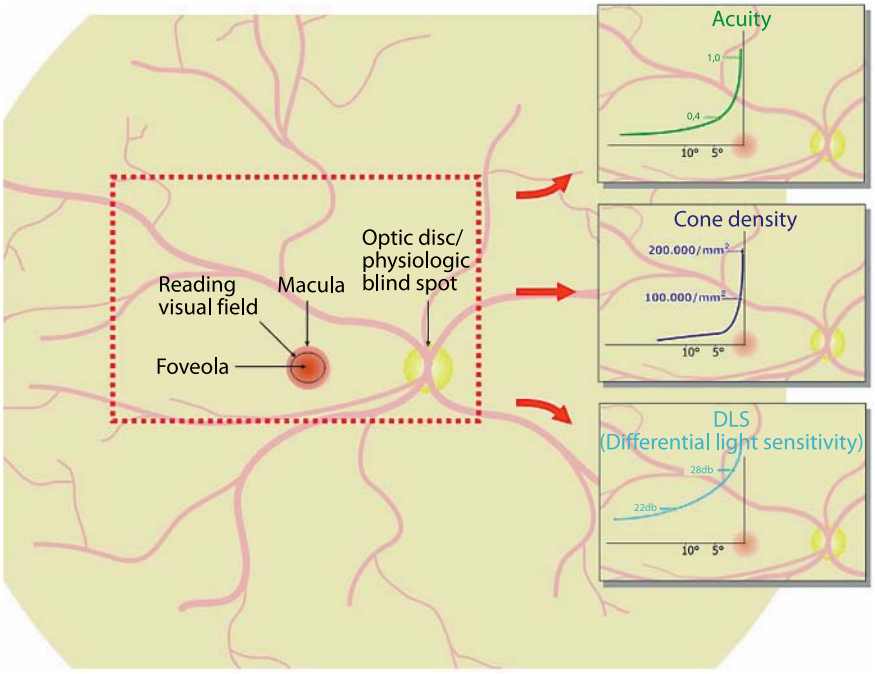


Fig. 3.2. Visual acuity, cone density and differential light sensitivity (*DLS*) as a function of visual field eccentricity (modified from Coren and Ward 2003, and Trauzettel-Klosinski et al. 1994; see "Further Reading")

First Neuron: Photoreceptors

The retina contains across its outer surface (about 12 cm^2) nearly 65 million photoreceptors per eye (see also Chap. 7): about 3.2 million cones and 60 million rods.

The areal density of photoreceptors falls rapidly from the fovea into the retinal periphery (■ Fig. 3.2). Efficient perimetric stimulus presentation considers these factors, using more closely spaced stimuli at the visual field center, with a rapidly decreasing density of stimuli for more peripherally located visual field areas. But even in the most peripheral parts of the retina, there are sufficient numbers of cones to dominate vision under photopic levels of illumination when the rods are completely bleached.

Pearl

Most of today's perimeters operate with an adapting background luminance of 3 to 10 cd/m^2 in the lower photopic range, and consequently, test the function of cone-initiated vision only.

Second Neuron: Bipolar Cells

In the human retina, "only" 10 million bipolar cells (see also Chap. 7) process the signals arriving from the approximately 65 million photoreceptors. The neural convergence found at this level of retinal circuitry is not homogenous: While the peripheral retinal regions operate with a comparatively sparse population of bipolar cells, the central portions of the retina (foveal and perifoveal macula) process the photoreceptor signals in a 1:1 or cell-for-cell arrangement. In other words, while there is high neural convergence in the retinal periphery, there is a parallel processing of the signals from the densely clustered receptors at the fovea and perifoveal macula.

Third Neuron: Retinal Ganglion Cells

The retinal ganglion cells give rise to axons that are about 75 mm in length (see Chaps. 8 and 12). They join one another at the optic disc to form the optic nerve, being myelinated only in their extraocular course. They pass through the optic chiasm with decussation of more than one half of the fibers to the contralateral side, and pass through the optic tracts to the lateral geniculate body, where they terminate.

Retinal Ganglion Cells and the Optic Nerve

The neuronal signals are concentrated into "merely" 1.2 million ganglion cells (per eye). Their axons form the retinal nerve fiber layer, just deep to the internal limiting membrane. They are characterized by a widely fanned-out shape that skirts the macula, and they then converge at the margin of the optic disc. Their spatial arrangement gives rise to a typical pattern when disease damages associated groups of fibers at the disc margins: The fibers arriving at the temporal sectors of the disc margin arise from cell bodies located either above or below the temporal horizon-

tal raphe, which they "respect," or do not cross, but form superior and inferior arcuate shapes that converge as they approach the disc.

Pearl

Damage to the retinal ganglion cells in the vicinity of the optic disc produces typical arcuate defects in the visual field that do not cross the nasal horizontal meridian, hence the so-called nasal step. The shape of an arcuate scotoma is similar to that of a scimitar; its hilt located at the physiologic blind spot and its tip at the nasal horizontal meridian. The fibers arriving at the disc from the temporal hemiretina (both superior and inferior arcuate groups) cross the borders of the disc at the superior and inferior poles. Bundles of fibers arriving from the nasal hemiretina form a more wedge-like shape with straight sides and the apex located at the nasal disc border.

The ganglion cell axons join one another to exit the eye through the optic disc, which is about 1.5 mm in diameter. In doing so, the fibers from the retinal locations that are closest to the disc rise to the retinal surface and enter the disc at its most central core. Fibers that originate in the retinal periphery, by contrast, course through the innermost portions of the nerve fiber layer, closest to the vitreous body. They exit the eye through the outermost portions of the optic disc, closest to its border (■ Fig. 3.3). Upon exiting the ocular wall through the lamina cribrosa, the axons acquire a myelin sheath, and the diameter of the nerve increases to 4 mm. The fibers are separated into about 300 to 1,000 bundles by connective tissue septae. The optic nerve has a floppy, sinusoidal course within the orbit, which allows the globe to rotate at high speeds and with minimal inertia. The optic nerve has an intraorbital length of 20 to 30 mm, an intracanalicular length of 3 to 8 mm, and an intracranial length of 3 to 16 mm. At the posterior extreme of the optic nerve, the afferent visual pathway acquires a new name, the chiasm, as the optic nerves merge with one another.

Pearl

The optic nerve is particularly susceptible to damage by space-occupying lesions within the optic canal. Masses of any kind arising in the canal will compress the nerve, and the rigid walls prevent any escape or decompression of the neural tissues.

Within the retina, the axons arising within the temporal hemiretina follow an arcuate path that skirts the macula above and below the horizontal meridian with the axons respecting (not crossing) the horizontal meridian. As they

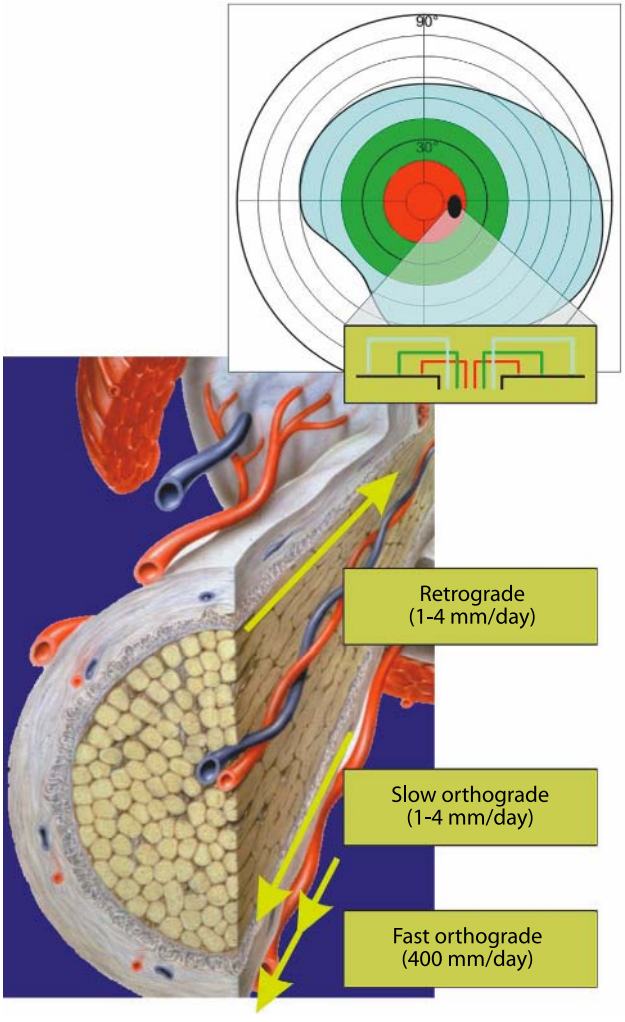


Fig. 3.3. Schematic diagram of the pattern created by the layering of the ganglion cell axonal nerve fibers in the nerve fiber layer of the retina and the corresponding visual field regions (upper insert) as well as the structures within the optic nerve and the axoplasmic flow parameters (modified from Krey et al. 1986; see "Further Reading")

Animation 3.1

pass into the optic nerve, the ganglion cell axons acquire a completely different organization, as they separate from one another according to their origins with respect to the vertical meridian. Axons from cells located to the nasal side of the vertical meridian (remember: the vertical meridian through the fovea, not the optic disc) decussate at the chiasm, while axons from cells located in the temporal hemiretina remain ipsilateral. The tight, septate axon bundles so highly organized in the optic nerve undergo reorganization at this point in the afferent pathway. They intermix in what seems to be a relative disorganized fashion, giving rise to a loss of the topographic organization of the visual field found with diseases of the retina and optic disc. Consequently, the perimetric spatial localization of disease is very poor for lesions of the intracanalicular optic nerve.

Nonetheless, perimetry remains a very important diagnostic tool for following the course of disease in this region.

The very thin fibers of the papillomacular bundle are clustered together in the core of the optic nerve, and they represent the largest number of fibers in the so-called parvocellular system. These axons project into the layers of the lateral geniculate body that contain neuronal somas, which are also quite small (see ■ Fig. 3.6). Parvocellular neurons transmit the encoded image information from the central-most portions of the visual field, which is characterized by high spatial resolution, good color perception, and stereopsis. This subsystem of the afferent pathway is particularly susceptible to demyelinating or toxic damage, resulting in defects of the central visual field – central scotomas.

Pearl

This central group of fibers from the papillomacular bundle occupies approximately 70% of the cross-sectional area of the afferent pathway in the optic nerve, chiasm, and optic tract. These fibers are also more sensitive to damage caused by space-occupying disorders, and their axonal transport mechanisms suffer, whether by direct mechanical compression of the fibers or impairment of their capillary blood supply (cf., ■ Fig. 3.3).

For this reason, it is generally the case that examination of the central 30° of the visual field is adequate for the detection of visual loss caused by the overwhelming majority of neuro-ophthalmic disorders that damage the anterior portions of the afferent pathway.

Optic Chiasm

The fibers that arise in the nasal hemiretinas of both eyes (nasal to the fovea-bisecting vertical meridian) decussate in the chiasm to the contralateral side, while the fibers arising in the temporal hemiretinas remain ipsilateral as they enter the optic tracts (■ Fig. 3.4). During embryonic development, this process is thought to be controlled chemotactically, so that there are no sharply defined or straight lines at the interfaces between adjacent groups of fibers. The neural bundles originating in the nasal hemiretinas – and which decussate to the contralateral side within the chiasm – form short loops that protrude into the proximal contralateral optic nerve (by the inferior half of the decussating

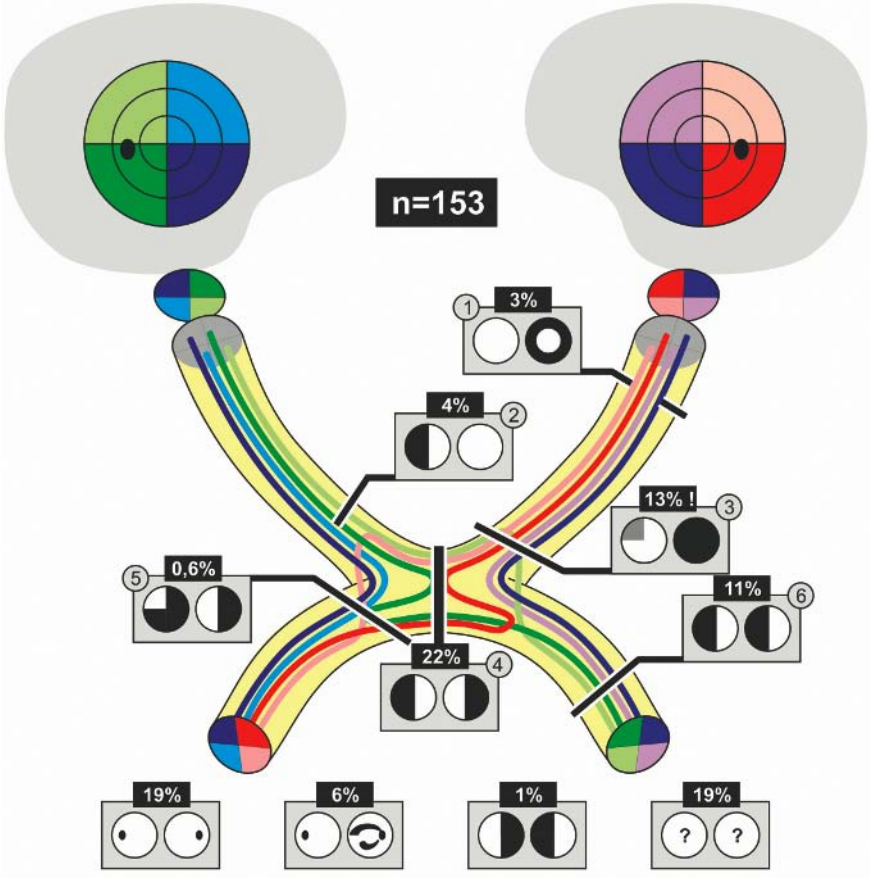


Fig. 3.4. Schematic diagram of the course of the ganglion cell axons in the region of the chiasm and the corresponding visual field defects with their frequency of occurrence. The effect of the more common lesions within the various visual pathway segments in the chiasmal region on the central 30° of the visual field are diagrammed as examples. *1* Compressive optic neuropathies. *2* Partial prechiasmal lesion. *3* Anterior junctional syndrome with subtotal damage to anterior Wilbrand's knee, which carries the afferent signals from the contralateral inferior nasal retinal fibers, which correspond to superior temporal visual field quadrant. This pattern is often found with advanced levels of damage or even complete loss of function in the ipsilateral optic nerve. *4* Disease of the central chiasmal region. *5* Posterior junctional syndrome with damage to the posterior knee of Wilbrand, which carries signals form the ipsilateral superior nasal retinal quadrant and represents the inferior temporal quadrant of the visual field. This ipsilateral defect is associated with a homonymous hemianopia to the contralateral side. *6* Lesion of the optic tract (from Schiefer et al. 2004; see "Further Reading")

Animation 3.2

axons) and into the ipsilateral optic tract (by the superior half of decussating fibers) before completing the transition to the contralateral optic tract, where they are joined by the fibers originating in the corresponding contralateral temporal hemiretina (for further details, please see the "Anterior Junction Syndrome" section below). The chiasm measures 8 mm from the anterior to the posterior commissure, and is about 12- to 18-mm wide and 4-mm thick.

Pearl

The chiasm is the locus of the greatest risk for catastrophic loss of vision. The sum total of visual information within the afferent pathway is concentrated into the small volume of about 1 cm^3, where it is maximally susceptible to damage by focal disease processes. Consequently, comparatively small foci of disease in this region can produce rapid and complete, bilateral blindness. The space-occupying diseases of the sellar region are numerous (■ Fig. 3.5). Most common is the pituitary adenoma, which arises from just beneath the chiasm, and which is the most common (and mostly benign) intracranial tumor (see Chap. 12). A point to keep in mind is that a tumor arising from the pituitary gland must rise a full 10 mm above the diaphragma sella before contacting the chiasm. After the advent of MRI scanning, it has become quite common for small adenomas to be detected long before they do visual damage, and their frequency is far greater than had been suspected.

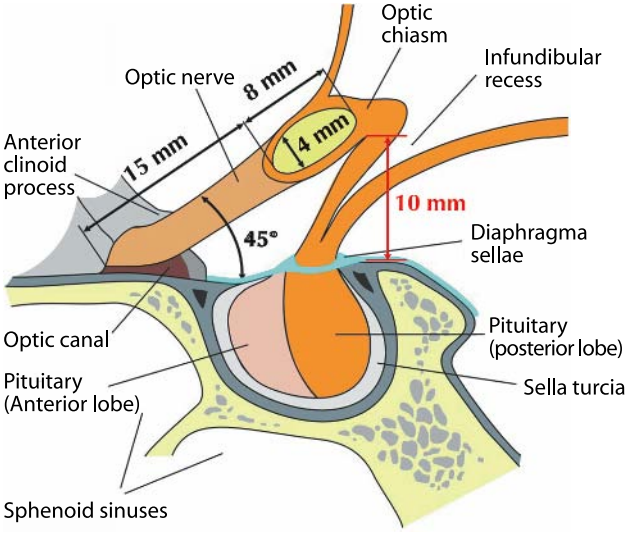


Fig. 3.5. Structures of neuro-ophthalmic relevance and their relative positions in the perichiasmal region (modified from von Lanz et al. 2003; see "Further Reading")

The relative positions of chiasm and hypophysis means, on the one hand, that microadenomas (by definition as intrasellar lesions) never cause perimetrically detectable visual field defects. On the other hand, when an adenoma has grown so large that it is detectable by the visual field defect it causes, it is already at an advanced stage of the disease (■ Fig. 3.5). Since the risk of pituitary apoplexy (intralesional hemorrhage with rapid expansion of the mass) increases as the tumor enlarges, visual field loss attributable to a pituitary adenoma always requires that an imaging procedure (preferably an MRI) be done quickly (see Chaps. 12 and 20).

There are other mass lesions in the sellar region that must be included in the differential diagnosis: meningiomas (tuberculum sella, sphenoid, clivus), and craniopharyngiomas (see Chap. 12). Anteriorly located are the paranasal sinuses that are at risk for bacterial infections and trauma, especially the neighboring ethmoid sinuses.

The carotid arteries and cavernous sinuses lie on each side of the chiasm, along with the oculomotor cranial nerves, the first and second divisions of the trigeminal nerve, and fibers of the sympathetic supply to the eye and orbit. Pituitary tumors can spread laterally to cause primarily motor pareses of the eye without any sign of damage to the afferent visual pathway (see Chaps. 10 and 12).

Superior to the chiasm is the floor of the third ventricle. Invading mass lesions are limited in their movement by the relatively immobile tissues above; in addition certain blood vessels in the chiasmal region (e.g., the anterior cerebral and the anterior communicating arteries) can produce deep, pressure-induced furrows in the chiasm along with corresponding deficits in visual function.

Pearl

Chiasmal lesions produce characteristic visual field deficits that show respect for the vertical meridian (in at least one eye) and can be monocular or binocular with widely varying asymmetries (■ Fig. 3.4). This typical asymmetry also explains why patients with chiasmal disease are commonly found to have relative afferent pupillary defects (see Chaps. 2, 5, and 12).

Case TES 1.1

Anterior Junction Syndrome

see also Animation 3.2

Definition

Anterior junction syndrome (syndrome of the anterolateral chiasm) presents as a combination of severe central visual loss in one eye and asymptomatic or subtle defects in the superior temporal visual field of the contralateral eye.

This unique and unmistakable pattern is attributable to an anatomic feature in the chiasm called Wilbrand's knee, which is a temporary detour taken by the inferior nasal crossing fibers into the proximal end of the contralateral optic nerve (■ Fig. 3.4, no. 3). The existence of this redundant loop has been called into question by several authors, believing that the loop seen histologically is an artifact of tissue preparation. If the knee is not a true morphological feature of the chiasm, one can plausibly conclude that axons are being displaced by local forces attributable to axonal loss or by the mass lesions compression of the chiasm and/or proximal optic nerve. This would at least make the common clinical findings of anterior junction syndrome comprehensible.

An asymmetric disorder affecting the anterior chiasm can produce complete amaurosis of the ipsilateral eye. It is important when finding that vision has recently been lost in one eye to examine carefully its contralateral partner. If one finds a partial loss of the superior portions of the temporal half of the contralateral field, this should be regarded as manifest evidence of a chiasmal syndrome, and if it has not yet been done, imaging of the chiasm is mandatory (■ Fig. 3.4).

Pearl

Every unexplained (even unilateral) loss of vision requires careful perimetric testing of the visual fields of *both* eyes.

Optic Tract

The decussation of the axonal bundles that originated in the nasal half of the retina causes them to associate with fibers arising from the temporal hemiretina of the contralateral eye, and identical visual field loci for both eyes are processed in the cerebral hemisphere that is contralateral to its homonymous hemifield. All postchiasmal lesions of the visual pathway (with one small exception) are characterized by homonymous visual field defects.

The optic tract, about 20 to 30 mm in length, is comparatively well vascularized. It is not commonly affected by traumatic or space-occupying processes. It is very unusual for visual field defects to be caused by disease in this location: About 4% of all homonymous visual field defects are due to tract disease.

Because of relative disorder among axon bundles in the immediately postchiasmal tract, disease in this locale produces rather incongruent homonymous (contralateral) hemianopic defects. A few weeks after their onset, these defects are accompanied by a characteristic, manifest, bilateral, asymmetric optic atrophy (see Chap. 8, ■ Fig. 8.23 and Chap. 19, ■ Fig. 19.6).

Tract lesions are usually accompanied by a relative afferent pupillary defect (see Chaps. 4, 5, and 12). The relative afferent pupillary defect (RAPD) is found in the eye contralateral to the lesion. This probably reflects the greater size of the temporal hemifield (processed by the nasal hemiretina of the contralateral eye), as compared with the nasal hemifield.

The proximity of the optic tract to the structures of the internal capsule explains the frequent association of somatic hemisensory loss ipsilateral to the homonymous hemifield defect.

Pearl

Tract lesions are characterized by:

- A contralateral relative afferent pupillary defect
- A contralateral, incongruous, bilateral, homonymous visual field defect
- A bilateral, asymmetric optic atrophy that appears with a latency of several weeks or months after the visual loss

Fourth Neuron

Lateral Geniculate Body: Synaptic Relay

The lateral geniculate body (LGB), or lateral geniculate nucleus (LGN), is the last synaptic component of the afferent pathway prior to arrival at the primary visual cortex. About 1.2 million tract fibers on each side project onto about 5 million neurons of the optic radiations, which constitute the last segment of the afferent pathway to the cerebral cortex. The lateral geniculate body has a unique onion peel structure, which receives the input signals from both eyes and processes the data in its various layers with a strongly retinotopic organization (■ Figs. 3.1, 3.6, and 3.7a).

The projecting axons of the retinal ganglion cells that carry the data for high spatial resolution, color perception, and stereopsis terminate in layers of the lateral geniculate body, having comparatively small cell somas (see the parvocellular system, ■ Fig. 3.6). The encoded data from receptors that respond primarily to moving stimuli are carried by fibers that have poor spatial resolution and are processed in layers of the lateral geniculate body having cell bodies that are large (see the magnocellular system, ■ Fig. 3.6).

Lesions of the lateral geniculate body are relative rare and are principally caused by vascular disease. The structural organization of the geniculate underlies the features

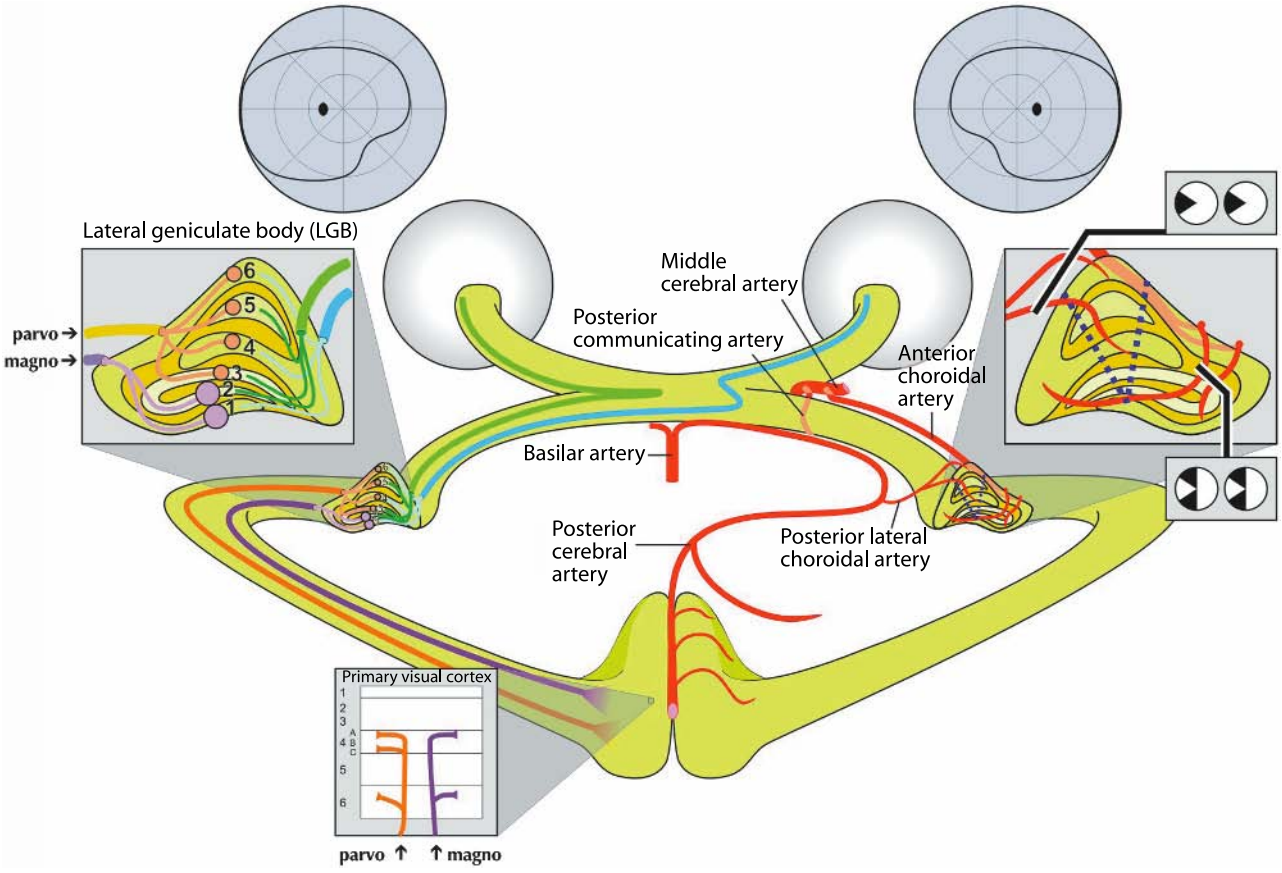


Fig. 3.6. Arrival of the third-order neuron axonal fibers innervating the layers of the lateral geniculate body (*LGB*) and their segregation into the magno- and parvocellular systems. *Left inset* Postsynaptic projection of the fourth-order neurons to layers (1–6/A–C) of the primary visual cortex. *Right inset* Blood supply of the lateral geniculate body and the corresponding visual field defects caused by subtotal infarctions of the geniculate nucleus

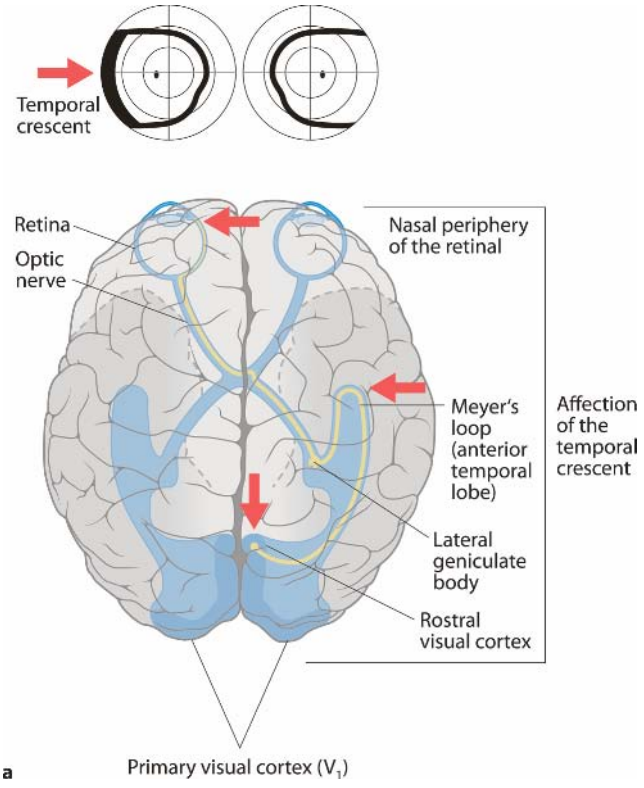
of its related visual field defects, which affect large portions of the central visual field with wedge-shaped, homonymous defects with relatively poor congruence (■ Fig. 3.6). Usually, these defects are associated with a contralateral RAPD when the lesions are located in the geniculate body or in a surrounding region of up to 16 mm away. When lesions of the postgeniculate fibers are located more than 16 mm away from the lateral geniculate nucleus (LGN), an RAPD is not usually present.

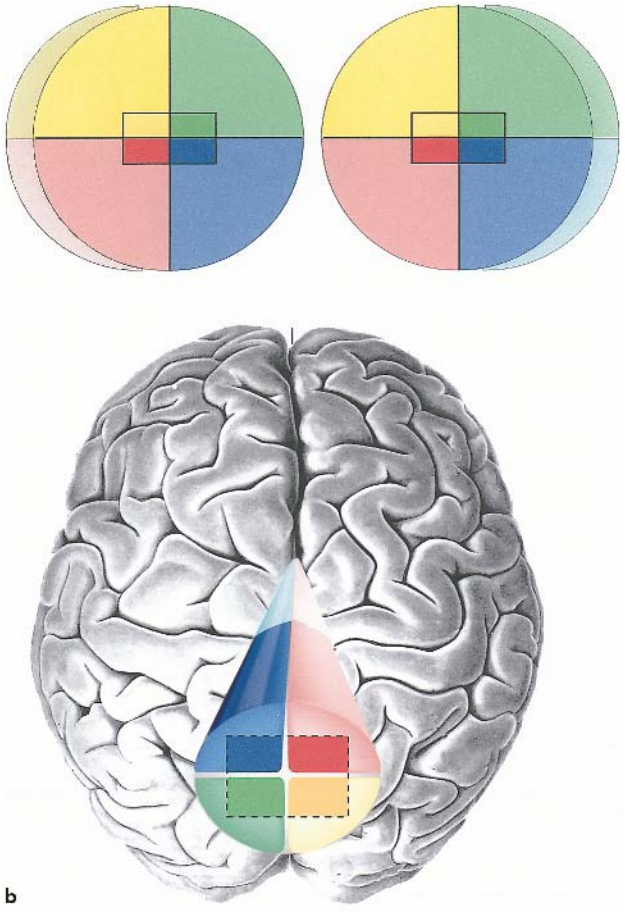
Optic Radiations

Shortly after leaving the geniculate body, the axons of the optic radiations fan out broadly to wrap around the temporal horn of the lateral ventricle. The fibers of corresponding retinal (and therefore of corresponding visual field) loci are located together in spatial proximity with one another and with a high degree of precision. This means that even small structural lesions will produce circumscribed, sharply marginated, absolute, congruent homonymous contralateral visual field defects. These characteristics are demonstrable with clinical perimetry, but only with instruments that control stimulus presentation with a high degree of spatial resolution.

Projection of this last neuron to the visual cortex appears to obey the all-or-none principle, since visual field defects of postgeniculate disease are almost always absolute.

Postgeniculate disease, i.e., damage to the optic radiations or visual cortex, is characterized by contralateral homonymous hemianopic visual field loss, which in contrast to lesions of the optic tract, are not accompanied by optic atrophy. This is because (at least among adults) there is no trans-synaptic degeneration at the lateral geniculate body.





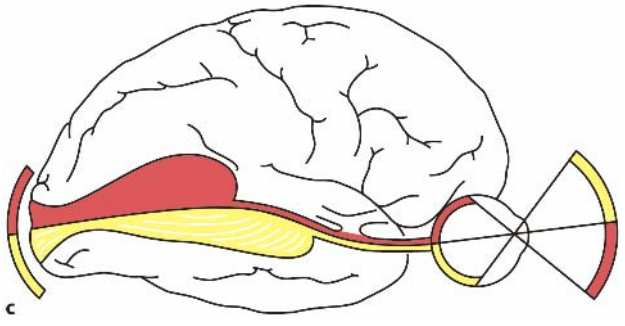


Fig. 3.7. **a** Sites of damage to the afferent visual pathway that are associated with visual field loss in the monocular temporal crescent (aspect of the brain as seen from above; modified from Zeki 1993; see "Further Reading"). **b** Schematic diagram of the relationship between the surface of the brain, the primary visual cortex, and the corresponding sectors of the human visual field (aspect as seen from above; also see ■ Fig. 3.8.) **c** The anterior and posterior portions of the afferent visual pathway with the corresponding portions of the visual field

Animation 3.3

Pearl

The comparatively uncommon homonymous scotomas in the inferior quadrants are associated with damage to the superior (parietal) portions of the afferent pathway. Conversely, homonymous defects in the superior quadrants are associated with disease in the inferior (temporal) fibers of the retrogeniculate pathway (■ Fig. 3.7 c).

Postgeniculate fibers of the afferent visual pathway that carry signals originating in the far periphery of the nasal retinal quadrants, i.e., the part of the visual field that is always monocular (the temporal crescent), participate in forming the so-called Meyer's loop. These fibers are found in the most rostral part of the loop, located near the apex of the inferior horn of the lateral ventricle (■ Fig. 3.7 a). These structures can be lost when the anterior portion of the temporal lobe is resected, e.g., when removing drug-resistant epileptogenic tissue, resulting in a homonymous defect in the superior quadrant of the contralateral visual field or a defect in the contralateral temporal crescent.

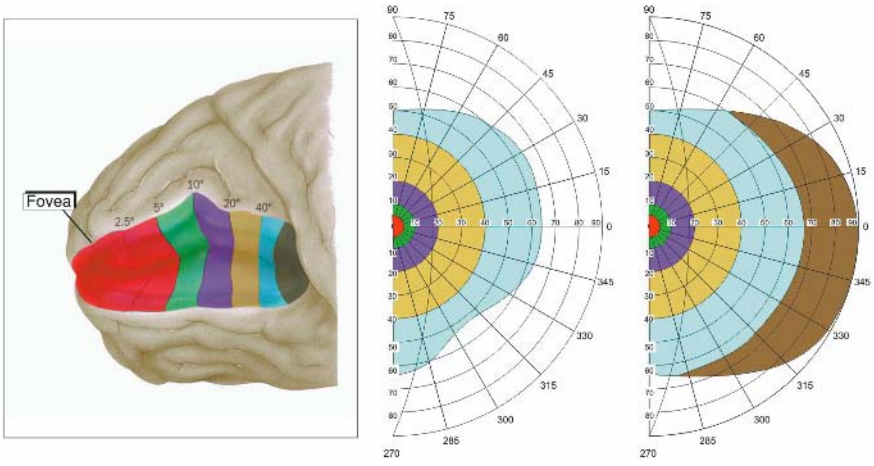


Fig. 3.8. The location and extent of (homonymous) visual field defects and their corresponding lesions within the visual cortex (modified from Walsh 1997; see "Further Reading")

! Note

Disease in the region of the anterior optic radiations (in Meyer's loop) indicates the need for careful examination of the peripheral visual field, by looking for a defect in the contralateral (monocular) temporal crescent (■ Fig. 3.7a).

Visual Cortex

The primary visual cortex (synonyms include calcarine cortex, area V_1, or area 17) with its complement of about 500 million neuronal cell bodies is the primary destination of the afferent visual pathways.

Having an area of about 30 cm^2 of cortical surface, the cerebral map of the visual field is considerably larger than that of the retina (about 12 cm^2). The visual cortex is the largest contiguous sector of the brain's surface that is devoted to a single sensory function.

Crudely simplified, the visual cortex forms the shape of a four-part cone with its basis at the occipital pole of the brain (■ Figs. 3.7b and 3.8). Lines of separation between the four parts include the interhemispheric fissure, separating right and left occipital lobes (and the right and left visual hemifields), and the calcarine fissures, which extend into the mesial aspects of the two occipital lobes, nearly orthogonal to the interhemispheric fissure (and separating the superior and inferior quadrants of each hemifield).

The primary visual cortex contains a retinotopic map of the visual field. About 50% of the cortical visual area is devoted to the central 5° of the visual field, corresponding to no more than 3% of the total visual field area. This high degree of cortical magnification in humans is illustrated by comparison of the red sectors in ■ Fig. 3.8.

The far periphery of the visual field, in the form of the two monocular temporal crescents, i.e., the entirety of the monocular portions of the visual field, is represented in the deeply situated, most anterior portions of the primary visual cortex, just posterior to the splenium of the corpus callosum and on the mesial surfaces of the occipital lobes. Each side, left and right, represents the monocular crescent of the contralateral eye (■ Figs. 3.7 and 3.8; also see Chap. 4).

! Note

When evaluating lesions in the region of the rostral visual cortex, perimetric study of the temporal monocular crescent is indicated (■ Figs. 3.7 and 3.8).

The occipital pole contains a region of collateral blood supply (a "watershed zone") along the boundary between the areas perfused by the posterior and the middle cerebral arteries. Homonymous hemianopias caused by cortical lesions are attributable to vascular disease in the vast majority of cases. For all lesions of the visual cortex, vascular disease accounts for 75% of all cases. Tumors are the next most common disease category in this region, amounting to 15% of cases.

Bilateral hemispheric lesions are not uncommon and produce homonymous defects in both sides of the visual field. If lesions in such cases are located above or below the calcarine fissure, the result can be bilateral altitudinal defects in the visual field that also appear to respect the horizontal meridian. Therefore, for example, a complete bilateral inferior hemianopsia (or bilateral, homonymous inferior quadrantanopsia) can be the result of bilateral hemispheric damage to the superior half of the postgeniculate visual pathway (■ Fig. 3.7b; see also Chap. 4). If on one side, the lesion occupies the superior half of the occipital cortex, above the calcarine fissure, while the contralateral lesion lies below the fissure, the result is called a checkerboard visual field (see Chap. 4).

Homonymous hemianopias can be divided into those that split fixation (total loss of one macular hemifield) and those that "spare" the macular region. It is thought that the tendency to spare the macular region (particularly for infarctions of the tissue supplied by the posterior cerebral artery) is related to the watershed zone phenomenon. When the macular cortical representation located at the posterior tip of the occipital lobe lies within a region of collateral supply from the middle cerebral artery, a significant portion of the macular hemifield can be spared. By convention, the term of macular sparing means that an area of at least 3° of radius from fixation has been spared. The pathogenesis and the topographical significance of macular sparing as a perimetric phenomenon have not been uniformly agreed upon. However, the functional significance is very meaningful: With macular splitting there is a profound impairment of reading fluency, while macular sparing usually preserves good reading fluency. Normal reading ability requires at least intact visual function in a small, horizontally oval area surrounding fixation: 2° to either side (right and left) and at least 1° above and below (see Chap. 24 for an extensive explanation).

Pearl

Postgeniculate lesions of the afferent visual pathway:

- Are not associated with optic atrophy when they are not congenital or acquired during infancy
- Are characterized by homonymous, mostly absolute, contralateral, binocular visual field loss
- Have an increasingly more pronounced congruence with locations approaching the primary visual cortex
- Are associated with reading disturbances when there has been loss of the central 2° of the affected visual hemifield
- Are caused by vascular disease in a majority of cases (particularly in the occipital region)
- Are associated (in as many as 30% of cases) with a relative afferent pupillary defect contralateral to the damaged hemisphere

Higher Visual Centers

Further processing of the neurally encoded visual data takes place in circumscribed and specialized cortical regions for specific modalities of vision (e.g., motion, color, etc.). Further, there are centers in the dorsal cortical regions close to the corpus callosum that have strong interhemispheric connections to corresponding structures in the contralateral hemisphere/visual hemifield. To be mentioned in this context also are connections to cortical regions with associative and mnestic functions, to those with motor and sensory language function, and to efferent visual brain centers (e.g., oculomotor accommodation).

A more compete discussion of the processing of visual sensation in higher centers can be found in Chap. 13).

Conclusion

Knowledge of the course, the neuronal organization, and the association with neighboring structures of the afferent visual pathways at their various neuronal levels (first through fourth neurons) is a fundamental prerequisite for understanding the topographic and pathogenic features of neuro-ophthalmically relevant visual disturbances.

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Chapter 4

Perimetry

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Examination of the visual field, whether on a hemispheric surface (in which case one is doing perimetry) or on a flat surface (where one is doing campimetry) is perhaps the single most important diagnostic test in neuro-ophthalmology.

Definition

By **visual field** we mean the sum total of all visual sensation experienced by on observer with a fixed head and torso position, with eyes steadily gazing at a stationary object. This is in contradistinction to *field of view* and *oculomotor fields*, in which it is understood that the head and eyes are allowed all freedom of movement. The visual field examination, in contradistinction to testing the pupils with the swinging flashlight test (see Chaps. 2 and 5), is not an objective test, but rather depends on the cooperation of the patient being examined. Given such cooperation, one can determine not only the depth of a defect, but also its size, shape, and location (■ Fig. 4.1). This is fundamentally important for topographic diagnosis (■ Fig. 4.2) and for monitoring the temporal course of lesions affecting the afferent visual pathway. This chapter describes the various methods of perimetric testing, provides a classification system (■ Fig. 4.3) of the visual field defects that are associated with neuro-ophthalmic disease, describes their various differential diagnoses, and shows which additional diagnostic tests they may indicate.

Poster 4.1
Poster 4.2

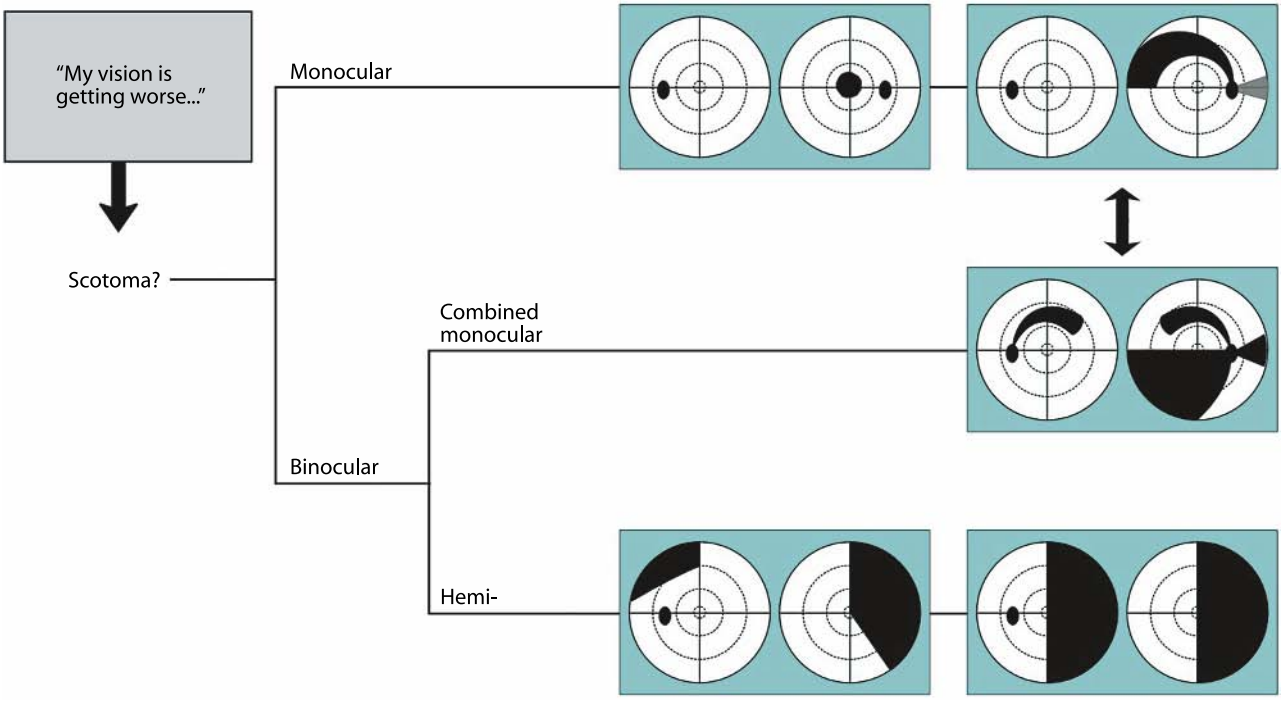


Fig. 4.1. The patient complaint, "My vision is getting worse," is consistent with many potential causes and types of visual field loss. Particularly significant is the fact that this sort of complaint can be produced by either monocular or binocular types of visual damage. This makes an initial examination of the visual fields *of both eyes* a necessary part of a complete neuro-ophthalmic examination

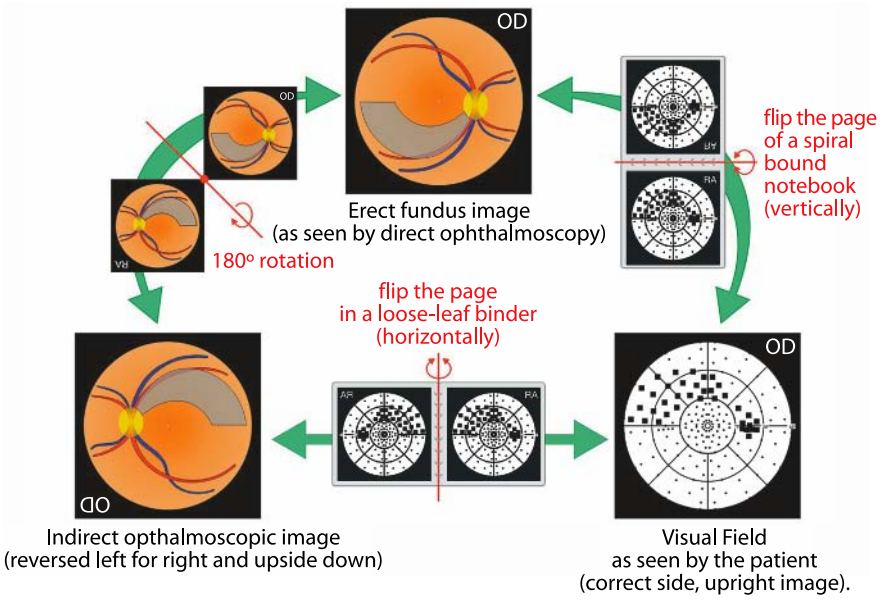


Fig. 4.2. Correlation between type of scotoma and location of disease in the visual pathway: If the defect lies in the *superior* half of the field, the causative lesion lies in the *lower* half of the retina or the *lower* half of the retrobulbar visual pathway, up to and including the primary visual cortex and vice versa. In addition, defects in the *nasal* half of the visual field correspond to the *temporal* hemiretina; the retinal ganglion cell axons originating there do not decussate at the chiasm, but remain in the ipsilateral half of the visual pathway. A defect in the *temporal* hemifield maps to the *nasal* half of the retina, and the axons arising there decussate at the optic chiasm, projecting to the contralateral lateral geniculate body and cerebral hemisphere. All lesions of the afferent visual pathway lie in positions that are the opposite of their corresponding visual field defect, i.e., the mapping between field defect and lesion is both horizontal and vertically reversed

Indications for Perimetric Testing

Perimetric testing should be considered appropriate when the following problems, findings, or factors are present:

- The presence of a relative afferent pupillary defect (RAPD)
- Monitoring of visual field defects already known to exist
- Signs or symptoms of damage to the afferent visual pathway
- Visual disturbances of unknown cause (e.g., for nyctalopia, loss of brightness perception, and disturbances of reading or of visual orientation)
- Abnormalities of ocular fundus (optic disc and retina)
- Certification of visual function for driving or occupational tasks

Initial Methods of Testing

Additional Historical Information

It is useful to ask patients specifically whether they have been aware of visual field defects (called positive scotomas) or changes in their field of view, such as metamorphopsia. One should also briefly inquire whether there have been episodic periods of visual loss that might indicate a problem with transient ischemic episodes (see Chap. 14).

Pearl

Temporary blurring of vision or passing bouts of darkening can be manifestations of the obscurations of vision associated with papilledema, or may suggest a problem with intermittent optic nerve compression. Not uncommonly, such symptoms begin as monocular, affecting one eye more heavily than the other, can be provoked with only minimal head movements, and indicate a disturbance of axoplasmic flow (see Chap. 3, ■ Fig. 3.3, and Chaps. 9 and 12).

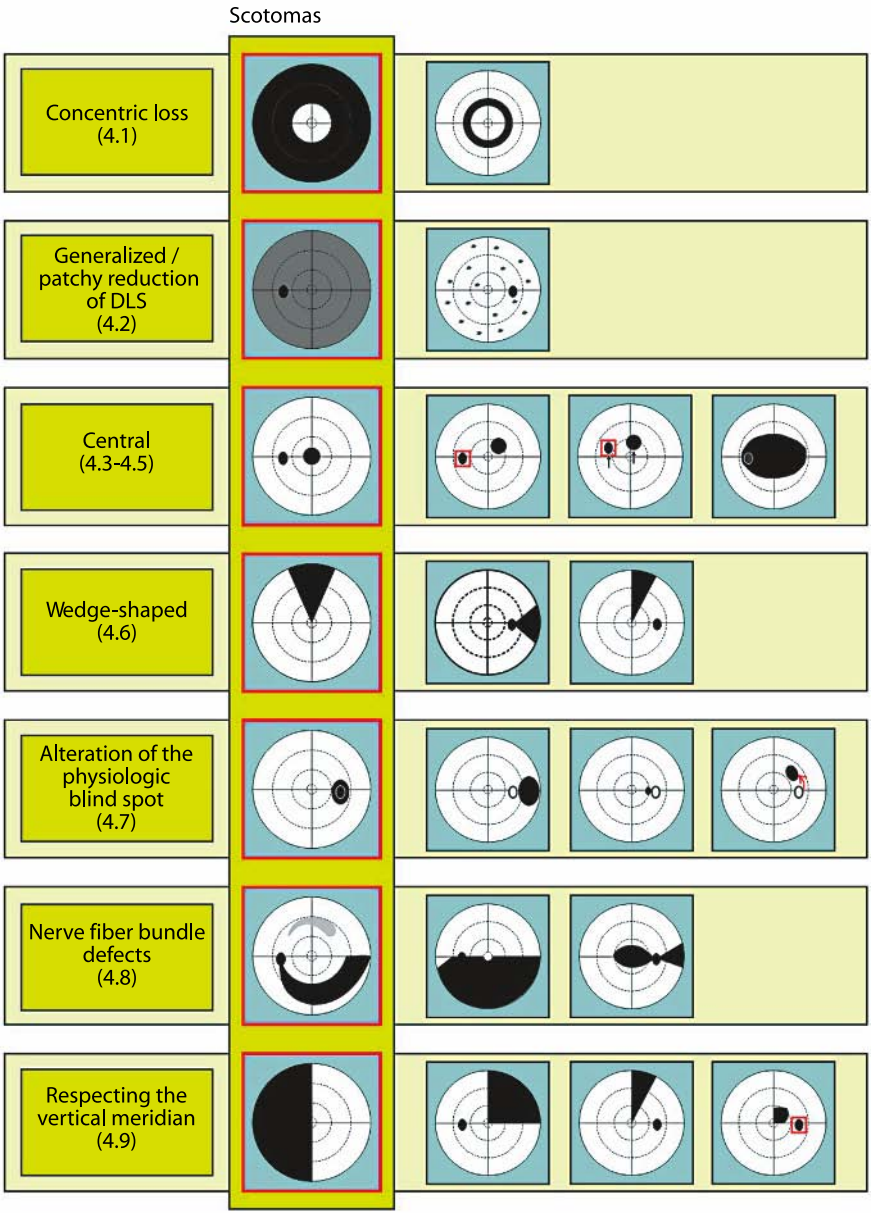


Fig. 4.3. Topologically diagnostic classification of scotomas (schematic diagram). Visual field defects have been divided into seven primary types (left side of diagram); in the *right half* of the diagram are commonly occurring subtypes. The *numerical labels* in the *left half* of the diagram refer to the corresponding numbers of the Compendium of Visual Field Defects. *DLS* Differential luminance sensitivity

Poster 4.1
Poster 4.2

Swinging Flashlight Test

Although the swinging flashlight test (see Chap. 2) is not a visual field test in the narrower sense, it should be used routinely as a quick and simple means of detecting afferent visual problems prior to a more thorough examination of the visual field. It can detect monocular or significantly asymmetric, bilateral disturbances of vision in the pregeniculate (anterior) portions of the afferent pathway, and is an objective method that does not depend on the patient's cooperation. The swinging flashlight test is indicated by any unexplained disturbance of vision, as well as by any suspicion of a lesion in the afferent visual pathway.

Confrontation Testing of the Visual Field

As an initial step in the examination, the hands or fingers of the examiner can be held (under steady control of fixation) in either or both halves of the visual field, but moved in only one hemifield at a time (■ Fig. 4.4 b).

Alternatively, when there is a suspicion of a hemianopic loss of field, the examiner can present both hands – held motionless – to either side of the vertical meridian, and ask the patient to report the total number of fingers being held out. This "finger perimetry" method can detect most widespread losses of the peripheral visual field, including hemianopsias and quadrantanopsias (■ Fig. 4.4 c).

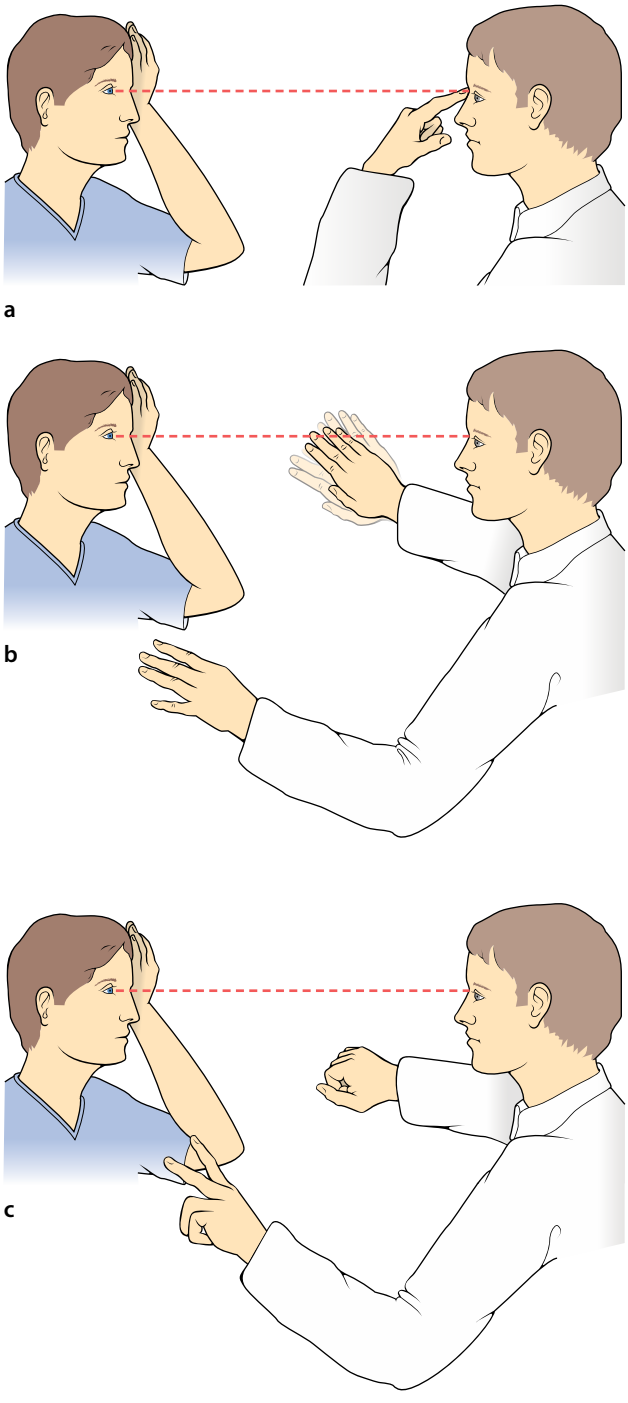


Fig. 4.4. Confrontation testing of the visual field **a** Maintenance of fixation (e.g., on the bridge of examiner's nose) is essential. **b** Bimanual testing of the visual field: The examiner closes the eye that is directly opposite to the eye the patient has closed and uses the field of his or her open eye's monocular perception as a basis for comparison to the patient's visual field, while presenting visual stimuli (e.g., moving one or both hands) in the opposing portion of the patient's visual field. This serves to reduce problems with fixation. **c** Counting of fingers held to either side of the vertical meridian tests the central visual field with relatively smaller "test objects", as compared with the bimanual tests

When examining small children, the examiner can maintain control of fixation while an assistant positioned behind the child introduces objects of visual interest into the various quadrants of the peripheral visual field. The child's head movements on detection of these stimuli allow a judgment of the intactness of the visual field.

Confrontation testing should be used routinely, when examining small children or uncooperative patients, whenever there is a suspicion of an advanced degree of visual loss. This preliminary method can also be put to use when circumstances do not allow use of conventional perimetric testing, such as at bedside consultations or in intensive care units. It also serves as a quick check of the plausibility of a patient's responses.

Pearl

A very effective modification of confrontation testing, useful in cases of homonymous visual field loss, has the examiner face the patient at a distance of about 30 in., while the patient fixes on the center of the examiner's face. The examiner then asks the patient whether the entire face is simultaneously visible. Missing portions of the face give an indication as to the extent of a homonymous defect. The closer a defect is to the vertical meridian, and the smaller is the remaining, congruous portion of the paracentral visual field (■ Fig. 4.5), the more likely there is to be a loss of reading fluency (see below).

Amsler Grid Testing

The Amsler grid is a visual field test that encompasses the central visual field to an eccentricity of 10°. It allows for the subjective detection and ongoing monitoring of retinal, primarily macular, diseases. The patient views an orthogonal grid of vertical and horizontal straight lines at a reading distance of about 17 in (40 cm). The grid has a central fixation point and is shown on a featureless background. It is a very effective test for the detection of metamorphopsia (e.g., caused by retinal edema or other disturbances of photoreceptor alignment), and its use can be delegated to the patient as a solo screening test.

The Amsler grid test is particularly useful when evaluating subjective symptoms of distorted images, reading problems, or signs of abnormal fundus appearance in the macular region. A small, printed figure of the grid can be given to a patient for self-monitoring of visual changes at home.

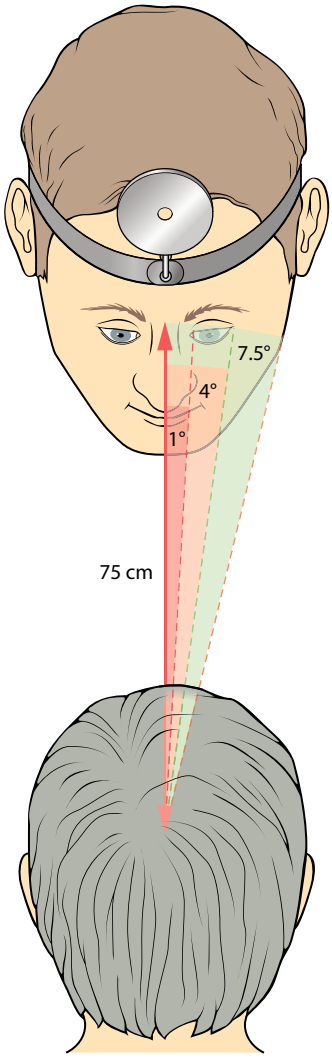


Fig. 4.5. Looking at and describing the examiner's face in the case of a homonymous visual field defect (the corresponding values for eccentricity at a distance of 75 cm [approximately 30 in.] are shown). If the patient with a hemianopic defect while fixing attention on the bridge of the examiner's nose can describe details only as far as the inner canthus of the examiner's eye, and all details peripheral to this locus are not seen, the visual field defect extends up to a point within 1° or less of fixation. In this case, reading ability will be significantly impaired

Reading Ability

Tests of reading ability, with an age-appropriate correction for near, are an effective method for examining a portion of the central visual field. Fluency of reading requires the normal function of a region at least 2° to the left and right and 1° above and below the point of central fixation (see Chap. 24). When a reading problem is found, a careful ophthalmoscopic examination of the macula will often reveal the cause, but if the ocular fundus is unremarkable in appearance, there is likely to be a homonymous hemianopic visual field defect that divides the central visual field, including the point of fixation and the perifoveal field on the affected side. Conversely, if there is a suspicion of a homonymous visual field defect, if there are any ophthalmoscopic signs of macular disease, complaints of reading problems or of amblyopia, tests of reading ability are a necessary part of the clinical evaluation.

Testing of Color Saturation

Testing of the symmetry of color saturation is best done with a brightly colored (red is usually best) object, such as the top of a mydriatic bottle. The object should be shown to one eye and then the other by slowly alternating monocular occlusion. When there is an optic neuropathy causing an acquired color deficit, the object seen by the affected eye will have a relative deficit of color perception, usually described by the patient as a "darker" or "faded" color, particularly when the object is held in an area of relative visual field loss (see Chaps. 2 and 6). Using the same colored object, confrontation perimetry can be done, while monitoring the patient's fixation, by holding the object in various locations in the visual field. Particularly noteworthy responses are descriptions of sudden change in the color's appearance, when the object is moved into or out of the region of a visual field defect. This can sometimes be quite striking, particularly when crossing the vertical meridian in instances of hemianopie deficits in the visual field.

In cases where optic atrophy is seen or an optic neuropathy is likely (as in patients with relative afferent pupillary defects), testing of color saturation by these simple methods is often very helpful (see Chap. 6).

Conventional Methods of Perimetric Testing

Pearl

When correlating visual field defects with lesions in the afferent visual pathway, it is helpful to keep in mind that the optical inversion of images in the eye causes an inversion of the visual field with respect to the afferent pathway. Thus, objects in the superior visual field are imaged in the inferior half of the retina, and the encoded data for that image remain in the fibers of the inferior half the pathway, at least for the optic nerves, the chiasm, and the retrogeniculate path. In addition, the temporal half of the visual field is imaged in the nasal fundus, etc. (see Chap. 3, ■ Figs. 3.4 and 3.7, and ■ Fig. 4.2).

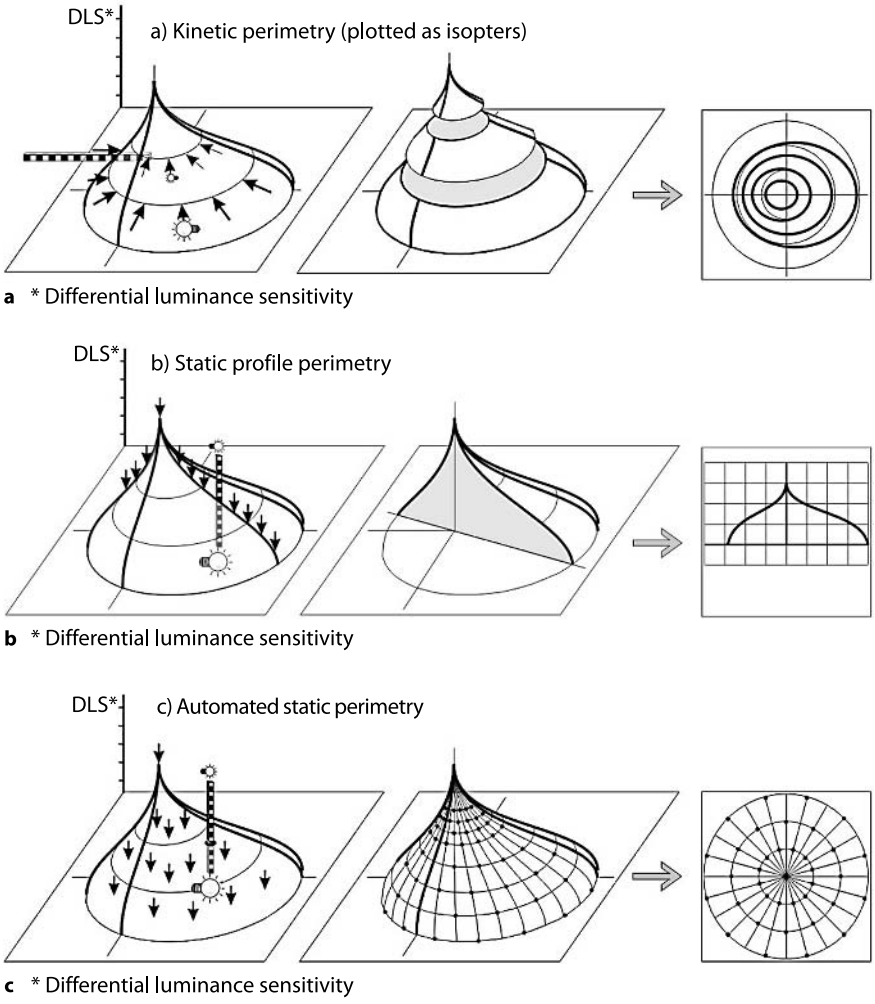
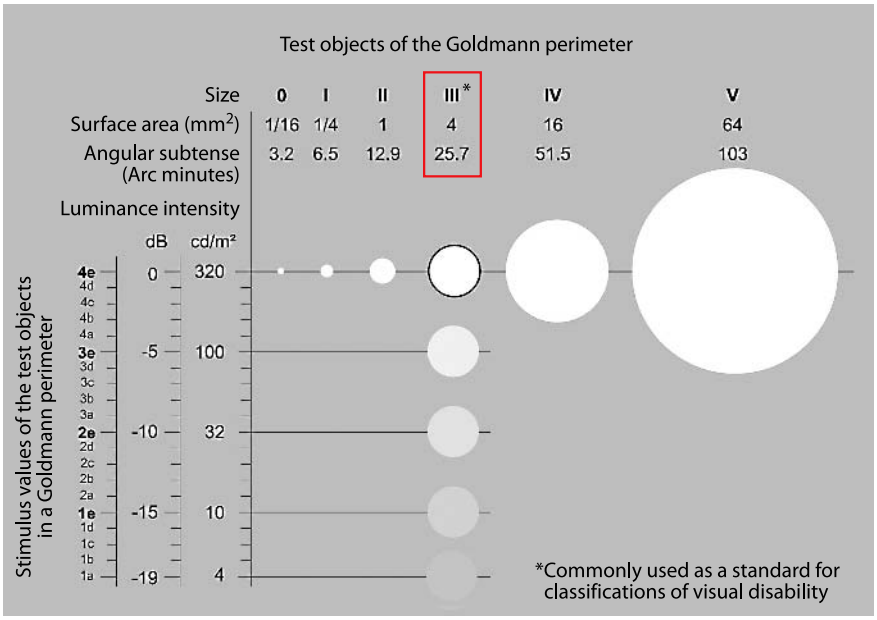


Fig. 4.6. **a** Conventional methods of perimetric testing: Kinetic perimetry (using test objects that are moved) yields results that are displayed as so-called isopters (lines of identical DLS that are comparable to a weather map's isobars). **b** Conventional methods of perimetric testing: Static profile perimetry (visual field testing with stationary test objects arrayed along a single meridian in the visual field) produces data that are displayed as a vertical profile of DLS that passes straight through the center of the field. **c** Conventional methods of perimetric testing. *Automated static perimetry*, in which static test object locations are distributed across a contiguous area of the visual field produces loci of DLS for each location in the pattern. Using these data, a virtual surface is computed, yielding a "reconstruction" of the hill of vision

There are two types of perimetry, kinetic and static. In kinetic perimetry, moving test objects are presented, while in static perimetry test objects are held in stationary positions when presented (■ Fig. 4.6). The common goal of these methods is to determine, as precisely as possible, the sensitivity of visual perception as a function of location in the visual field. The correct physiologic term for sensitivity is differential luminance sensitivity ([DLS] also incremental luminance sensitivity). These terms arise from the use of a background light to maintain uniform dark/light adaptation in all visual field areas, while test objects (small spots of light) are projected onto the background, thus adding their luminance to that of the adapting surround. The stimulus strength is expressed as a function of the incremental addition of the stimulus light to the adapting surround on which it is projected. Definitions and descriptions of related physiologic terms in perimetry are listed in ■ Tables 4.1 and 4.2. Three-dimensional reconstructions of the spatial distribution of visual sensitivity produce a conceptual "hill of vision" (■ Fig. 4.6). Radial lines extending from the visual field center are termed meridians (■ Fig. 4.6 c). Their angles of meridional orientation are analogous to those of the geographic meridians of the globe.

The currently accepted definition of the differential luminance sensitivity is related to the perimeter-specific maximum stimulus luminance capacity, complicating any comparison of results between differing instruments (■ Fig. 4.7). It made more sense to adopt a standard of reference in which the adapting background (surround) luminance level was agreed upon and held constant for all instruments. The level of 10 cd/m^2 was accepted, which is a low photopic level of retinal adaptation.

Table 4.1. Sizes and luminance intensities of the test objects used by the Goldmann perimeter



Kinetic Perimetry

When using kinetic perimetry, the examiner presents stimuli that move with a constant angular velocity and a constant brightness and size – the corresponding physiologic terms being *luminance intensity* and *angular subtense* (for additional help and definitions, see ■ Tables 4.1 and 4.2). The stimulus is projected onto a matte surface of uniform light intensity that serves as an adapting background. The test objects (the projected light stimuli) are moved from nonseeing to seeing areas of the visual field, as perpendicular as is possible to the expected peripheral boundaries of perception (■ Fig. 4.6 a).

An *angular velocity* of 4°/s is regarded as an optimal compromise between spatial resolution on the one hand and examination duration on the other.

Multiple presentations with a constant stimulus value detect contours of isosensitivity, comparable to the isobars of meteorological maps, and are called isopters (■ Fig. 4.6 a). Each isopter is tested within at least eight evenly spaced meridians, with stimuli moving from the periphery toward the center of the visual field. By choosing appropriate stimulus sizes and luminous intensities, the hill of vision's (conceptional) three-dimensional shape and size can be documented by plotting the various isopters. Kinetic perimetry is suited to the documentation of visual function for certification of visual performance, e.g., as necessary for safe operation of a motor vehicle. It is particularly suited to the examination of patients capable of only poor cooperation, permitting a high level of efficiency when examining large visual field defects.

Pearl

A common stimulus used for certification examinations is the III/4e test object, which has an angular size of about 26′ and a luminance of about 320 cd/m². This stimulus should be used in all kinetic perimetric tests so that the results of the various examinations can be more easily compared to one another.

When testing the physiologic blind spot, the usual test object is the I/4e, having a size of 6.5′ and a luminance of 320 cd/m². For diagnostic testing, the most discriminating (and therefore most significant) test objects are those of low luminance and small size. These are best suited to the detection of subtle, relative central and paracentral scotomas.

The dimensions of the test objects in the Goldmann perimeter are listed in ■ Table 4.1, and their luminance levels are given in ■ Fig. 4.7.

Static Profile Perimetry

For static profile perimetry, test objects are held in stationary positions, and their luminance levels are varied. The various locations are arrayed along straight lines that pass through the field center, and the choices of lines are determined by the regions of interest in the central and paracentral parts of the visual field (usually within 30° of eccentricity). Profiles of the island (or "hill") of vision (■ Fig. 4.6 b) are produced. This method of testing is no longer in general use, but remains a particularly good technique for

Table 4.2. Computational definitions of perimetrically relevant physical and psychophysical terms

Term	Definition	Symbol or abbreviation	Unit	Calculation	Examples
Luminance (*L*)	Absolute level of light intensity	*L*	Candela/m² (cd/m²) Apostilb (asb) Decibel (dB)	Conversion: $L\ (\text{asb}) = \pi \times L\ (\text{cd/m}^2)$ $L = 10 \times \log \frac{L\ (\text{cd/m}^2)_{\text{brightest test object}}}{L\ (\text{cd/m}^2)_{\text{current test object}}}$	Twilight = 0.1 cd/m² monitor screen = 200 cd/m² full sun on white surface = 10,000 cd/m² *L* of brightest test object = 1,000 cd/m², *L* of current test object = 10 cd/m², corresponding to 10 × log100 = 10 × 2 = 20 dB
Threshold luminance	Barely perceptible luminance difference between projected test object and adapting surround	ΔL_{min}	cd/m²	$\Delta L = L_{\text{test object min}} - L_{\text{surround}}$	Threshold luminance = 1 cd/m²
Decibel	Relative units for measures of physical intensity (particularly for *attenuation* of luminance)	dB[a]	A dimensionless measure of relative quantities	Measured value (dB) = $10 \times \log \frac{\text{reference value}}{\text{measured value}}$	+30 dB corresponds to 0.001 of the reference value −3 dB corresponds to a double of the reference value −20 dB corresponds to the 100fold of the reference value
Differential luminance sensitivity (DLS)	A measure of the visual ability to detect *differences* in luminance (between test object and adapting surround)	DLS	dB	$\text{DLS} = 10 \times \log(L_{\text{max}} \div L_{\text{test object}})$	A threshold luminance of 1 cd/m² corresponds to a DLS of 30 dB in the case of a perimeter with a maximal test object luminance of 1,000 cd/m²
Absolute visual field defect	Failure to detect the brightest test object of a given perimeter		Usually expressed as dB		E.g., failure to see a test object with a luminance of 1,000 cd/m²; *alternatively*, a local DLS that is >20 dB below the age-corrected norm
Relative visual field defect	Reduced DLS, but with retention of some degree of measurable visual sensitivity		Usually expressed as dB	Difference between normal and measured DLS	Normal local DLS e.g.: 25 dB measured DLS: 17 dB relative defect: 8 dB

L luminance, *DLS* differential luminance sensitivity, $L_{\text{test object min}}$ minimal luminance of the test object, L_{max} maximum luminance of test object for a given perimeter, L_{normal} age-corrected threshold luminance for a given test object, $L_{\text{test object}}$ luminance of the current test object, L_{surround} luminance of adapting surround

[a]Originally used for measures of relative sound intensity, the decibel (one tenth of a logarithmic unit, the bel) has been adopted for use by other psychophysical disciplines

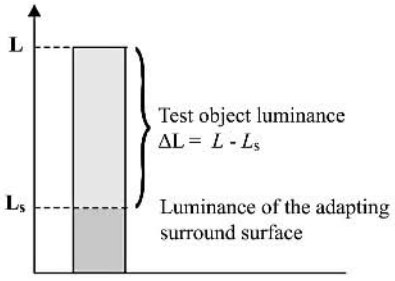
Scaling of test objects for various perimeters							
Differential luminance sensitivity (DLS)* in decibel (dB) units						Absolute values of stimulus luminance (ΔL)	
	Goldmann	TMP	TAP Twinfield	Humphrey	Octopus	asb [apostilb]	cd/m² [candela/m²]
Surround L_s [cd/m²]	10	3.14	10	10	1.26		
					47	0.02	0.01*
					46	0.03*	0.01*
					45	0.03*	0.01*
					44	0.04	0.01*
					43	0.05	0.02*
					42	0.06	0.02*
					41	0.08	0.03*
		40			40	0.09	0.03
		39			39	0.13	0.04
		38			38	0.16	0.05
		37			37	0.2	0.06
		36			36	0.25	0.08
		35	40		35	0.31	0.10
		34	39		34	0.41	0.13
		33	38		33	0.50	0.16
		32	37		32	0.63	0.20
		31	36		31	0.79	0.25
		30	35	40	30	1.01	0.32
		29	34	39	29	1.27	0.40
		28	33	38	28	1.57	0.50
		27	32	37	27	1.98	0.63
		26	31	36	26	2.48	0.79
		25	30	35	25	3.14	1.00
		24	29	34	24	3.96	1.26
		23	28	33	23	5.00	1.59
		22	27	32	22	6.16	1.96
		21	26	31	21	7.89	2.51
		20	25	30	20	9.93	3.16
	1a	19	24	29	19	12.50	3.98
	1b	18	23	28	18	15.74	5.01
	1c	17	22	27	17	19.82	6.31
	1d	16	21	26	16	24.94	7.94
	1e	15	20	25	15	31.40	10.0
	2a	14	19	24	14	39.5	12.5
	2b	13	18	23	13	49.7	15.8
	2c	12	17	22	12	62.2	19.9
	2d	11	16	21	11	78.9	25.1
	2e	10	15	20	10	99.3	31.6
	3a	9	14	19	9	125.0	39.8
	3b	8	13	18	8	157.4	50.1
	3c	7	12	17	7	198.2	63.1
	3d	6	11	16	6	249.5	79.4
	3e	5	10	15	5	314	100
	4a	4	9	14	4	395	125
	4b	3	8	13	3	497	158
	4c	2	7	12	2	626	199
	4d	1	6	11	1	789	251
	4e (L_{max})	**0 (L_{max})**	5	10	**0(L_{max})**	993	316
			4	9		1250	398
			3	8		1574	501
			2	7		1982	630
			1	6		2495	794
			0 (L_{max})	5		3141	1000
				4		3955	1258
				3		4979	1584
				2		6268	1995
				1		7891	2511
				0 (L_{max})		9934	3162

Explanatory comments

* Computation of the differential luminance sensitivity

DLS [dB] = 10 × log(L_{max}/|ΔL|)

The values of luminance intensity for the various test objects (ΔL) is computed as the difference between the photometric values (L) for a test object and the luminance of the adapting surround light (L_s) so as to yield a true "stimulus value", i.e, the luminance increment above the adapting background luminance.



Logarithmic scaling of stimulus values (10 dB = 1 log unit)

1dB ≙ $10^{0.1}$ = 1.26
2dB ≙ $10^{0.2}$ = 1.59
3dB ≙ $10^{0.3}$ = 1.96
4dB ≙ $10^{0.4}$ = 2.51
5dB ≙ $10^{0.5}$ = 3.16

Conversion between units of apostilb and candela/m² by the factor π = 3.14

0 dB = reference value of the dB scale corresponding to the maximum luminance intensity of the test object.

(Take note of the differing reference values for the various perimeters). Also, whereas the Octopus perimeter has the largest dynamic range, the Humphrey instrument produces the highest level of absolute luminance intensity.

Fig. 4.7. Comparison of the units of stimulus intensity for various perimeters. In the *left-hand column* are values for the comparable test objects of the Goldmann perimeter. *TMP* Tübingen manual perimeter, *TAP* Tübingen automated perimeter.
* Some absolute values of stimulus luminance are identical due to rounding error (for the remainder, please see the listing in ■ Table 4.2)

defining the locations and depths of small scotomas, and can be used for sequential exams to follow the course of the profile along the changing boundaries of scotomas or even at the foveal projection at the visual field's center.

Automated Static Perimetry

Automated static perimetry was developed as a logical extension of static profile perimetry. The profile technique was actually done manually by examiners that were skilled in the control of stimulus values, manually moving the controlling levers in conventional perimeters then being used for kinetic testing. The advent of microprocessors was the enabling technology for further development of the static methods. The manual technique was too complex for use in patterns of more than a linear sequence, but with the automated algorithms of the microprocessor, patterns of arbitrary complexity could be exploited. Quadratic grids of test locations evolved as the most frequently applied patterns. At each location within the grid of sites being tested, the automated methods determine the threshold of differential luminance sensitivity (■ Fig. 4.6 c). This approach yielded immediate improvements by allowing for a complex randomization of stimulus presentations. This means that several locations can be measured simultaneously, rather than determining threshold at one location before moving on to the next.

Strategies of Perimetric Testing

Two primary strategies for automated static perimetry have been developed (■ Fig. 4.8). In *threshold static perimetry* (■ Fig. 4.8, left side), stimulus intensity is varied for each location in the testing grid, as a function of the patient's responses. Using this type of strategy allows for a rather precise determination of the depths of a defect, although at the cost of multiple stimulus presentations and/or an increased density of stimulus locations.

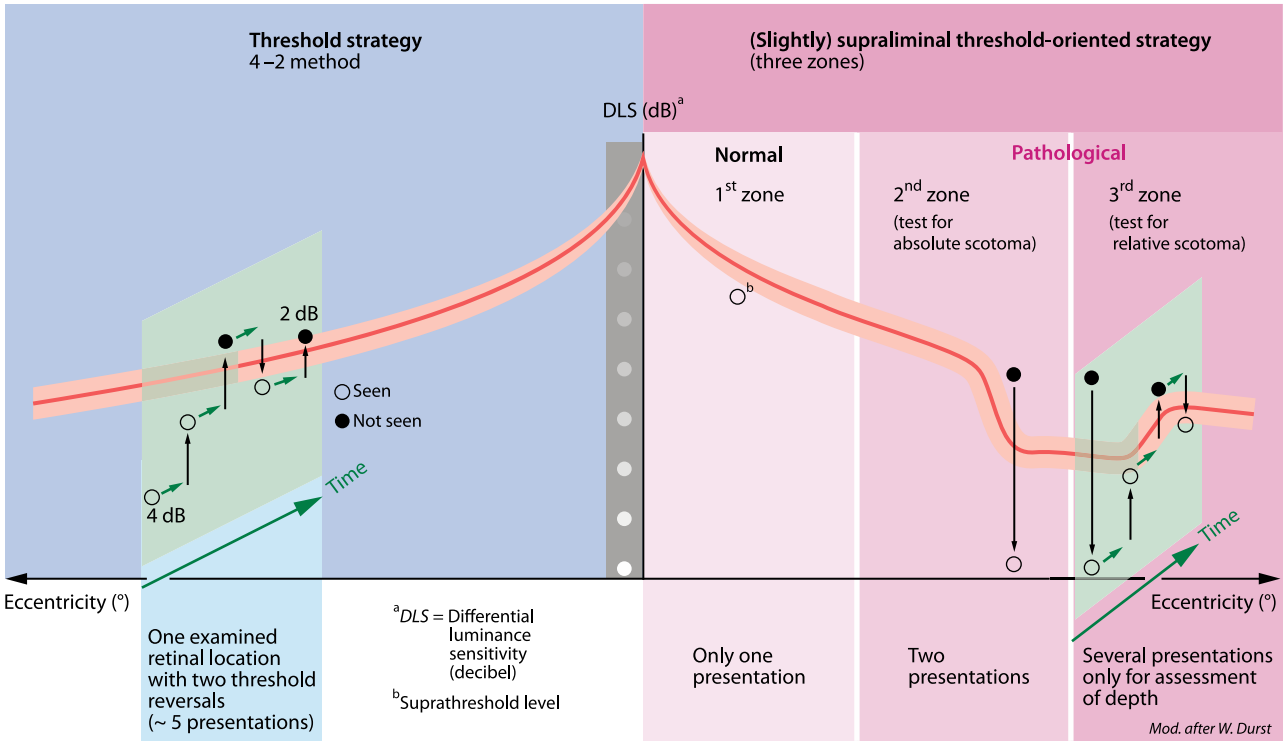


Fig. 4.8. Testing strategies used with automated static perimetry. *Left* The principle of *threshold static perimetry*, in which the threshold for perception of a stimulus is determined by sequentially presenting test objects with stimulus values that lie just above or below a putative value at a given location, and threshold is defined as a probability of perception of 0.5. Threshold determination requires a large number of stimulus presentations at each location and costs a comparatively great deal of time, which patients find very tiring. *Right* The principle of *slightly supraliminal static perimetry*, in which stimuli are presented with differential luminance values that are just above expected threshold (based on age-corrected data). If the patient detects a stimulus presentation, no additional stimuli are used at that location, but if the stimulus is not seen, a stimulus of maximal intensity is presented at the location. One of three potential levels of response is thus detected at each site: normal, a relative deficit, or a maximum luminance defect. This method uses a much shorter length of testing time, making it much easier for the patient. Subtle depressions of the local DLS are more likely to go undetected by this method

Supraliminal static perimetry, the second primary strategy (■ Fig. 4.8, right half), differs by presenting test objects that are intentionally above the expected threshold at each location. If the patient responds to the presentation of a test object, it is assumed that visual function is intact, and that location is not tested again. If the patient fails to respond at a given location, a test of the location is repeated with maximal stimulus intensity. If the patient fails to respond to the maximal intensity stimulus, an absolute scotoma is inferred, while a response to the brighter stimulus suggests a relative scotoma at that location. This method is relatively quick and places a minimal burden on the patient's ability to perform, but will also miss detection of shallow relative scotomas that may be of clinical importance. On the other hand, the supraliminal strategy allows for a comparatively greater number of test locations and a correspondingly higher degree of spatial resolution. This latter property is particularly important for topographic localization of defects in neuro-ophthalmology. It permits a more precise determination of the location and size of scotomas and well as their positions relative to important structures of reference, such as the vertical and horizontal meridians and/or the physiologic blind spot.

Pearl

A particularly appropriate pattern for testing patients with neuro-ophthalmic disorders is a grid of stimulus locations that increases in spatial density (becomes more crowded) as the center of the field is approached. This matches the visual field's physiologic property of maximal spatial resolution at the foveal projection with steadily decreasing resolution as a function of eccentricity. In addition, an increased number of test sites that straddle the horizontal and vertical meridians permits a more sensitive detection of defects that "respect" these boundaries. Such defects are common in the presence of chiasmal and/or retrochiasmal disease.

Absolute and Relative Visual Field Defects

Definition

An **absolute visual field defect** is present at any given location, if the I/4e test object (10′ of angular size and 320 cd/m^2) or any higher stimulus value is not seen. Another definition judges an absolute defect of the increment luminance sensitivity as one that is reduced by 20 dB (i.e., 2 log units), relative to the age-corrected norm at the same location.

A **relative scotoma** is one in which the standard test object (I/4e) is seen, but the expected level of light increment sensitivity is not fully achieved.

Sources of Error and Important Prerequisites for Perimetric Testing

As in all forms of psychophysical testing, the visual field examination should not be interrupted by disturbances in or around the room in which the examination is being done. Noise or audible background interference and intrusion by stray sources of light in the instrument cupola are just as important as the patient's comfort during the examination.

The patient must be carefully instructed as to how he/she is to cooperate in the examination. The task of divided attention (which is not familiar to inexperienced patients), the probable sequence of events, and the expected duration of the test should be reviewed. The presence of the examiner is required throughout the examination, so that signs of fatigue – such as gradual sinking of the upper lid, pupillary miosis, or poor fixation maintenance – can be detected. Intervention to motivate the patient, even with frequent interruptions of testing, is preferable to the risk of accepting unreliable responses.

Pearl

Examination of the visual field periphery (for all eccentricities greater than 30°) can be done with no optical correction. Within the central 30° of the field, however, an appropriate correction is required. Suitable lenses (with very narrow frames) should be used. The lenses should include an age-corrected addition for the distance between eye and cupola surface and a correction for any astigmatic error of one diopter or more.

To keep the spherical lens as thin as possible, cylinders of both plus and minus series should be available. Transposition of spherocylindrical notation between equivalent corrections then allows selection of the lesser spherical power, e.g.:

+2.0 sphere –3.0 cyl | 70°
corresponds to
–1.0 sphere +3.0 cyl | 160°.

Given the relatively poor stimulus for accommodation inside the instrument cupola, an age-appropriate near correction for the distance between the eye and the hemispheric surface of the cupola should be used, as summarized in ■ Table 4.3.

Fine-tuning of the near correction can profit from the patient's input, and the power of sphere and cylinder used for the test should be recorded.

Table 4.3. Perimetric corrections for near (rules of thumb)

Outside of the central 30° of field: • No correction
Within the central 30° of field: • Sufficient correction for the test distance, depending on the cupola radius of the perimeter • Lenses with very narrow rims • Correction for astigmatic errors of one full diopter or more
Near addition for patients starting at ages 35 to 40 years (in case of a cupola radius of 33 cm): • Age 35 to 50 years: use an addition of +1 diopter sphere • Age 50 to 60 years: use an addition of +2 diopters of sphere • Age over 60 years: use an addition of +3 diopters of sphere

Controls for the Quality and Plausibility of Perimetric Results

Controlling Fixation

The examiner should maintain direct and continuous supervision by means of a telescopic sight or video monitor. It would be ideal to document the quality of fixation during each presentation of the stimulus. During automated examinations, an indirect form of control for fixation is the use of so-called catch trials. This is done by presenting suprathreshold stimuli into the center of the previously mapped physiologic blind spot (the so-called Heijl-Krakau method). This strategy is of limited use when the blind spot is significantly enlarged or when the determination of the blind spot location is inaccurate.

! Note

The physiologic blind spot can in general serve as a reference scotoma or criterion of the test's validity: If it cannot be detected and documented as an absolute scotoma, the validity of the examination's findings will be markedly reduced.

An alternative type of automated fixation monitoring uses random presentations of stimuli that are minimally suprathreshold at the center of the field. The patient can see these presentations only if he/she is truly maintaining central fixation. An inaccurate determination of the threshold at fixation can of course produce invalid results when using this method.

Detection of False-Positive Responses

To test for false-positive responses several exclusively auditory stimuli can be presented during the course of the examination. These are meant to detect reflex responses that are not truly visually dependent. Frequent false-positive responses indicate a risk of underestimating the depth or size of a scotoma or area of depressed visual sensitivity, and can even result in failure to detect significant areas of visual field damage.

Detection of False-Negative Responses

To detect false-negative responses (instances of failure to respond to suprathreshold stimuli), strongly suprathreshold stimuli are presented at various locations within the visual field where prior determinations of threshold have already been completed. A high number of such falsely negative responses suggests marked variations in the patient's ability to concentrate or in the visual field performance itself, and could lead to an overestimation of the size of a scotoma, or even produce a false indication of visual field loss.

Usually, about 10 to 15% of stimulus presentations are divided evenly among the catch trials and the trials of false positive and false negative responses.

Pearl

Visual field test results are of limited value when any one of the three types of controlling trials produces faulty responses in 20% or more of its presentations.

Display of the Test Results

To make best use of the test results, it is particularly important that all of the test data are documented, including the optical correction used, the acuity of the eye with best correction, the results of catch trials (see above), and the time and duration of the test. For automated threshold static perimetry, the results of stimulus presentation within the physiologic blind spot, as well as in the area immediately surrounding the blind spot, should be provided, if this area can fulfill its important role as a reference scotoma (see above).

Isolated grayscale plots of the results are inadequate, since the borders of scotomas are interpolated in such plots, can frequently yield inaccurate impressions, and can even mask the presence of clinically significant defects. For this reason the location of all points in the pattern of test objects should be overlaid on the grayscale plots

Pearl

Preferably, the presentation of the data for both eyes should be shown side by side for simultaneous viewing (the left eye's field on the left and the right eye's field on the right) – exactly as seen by the patient.

Poster 4.2

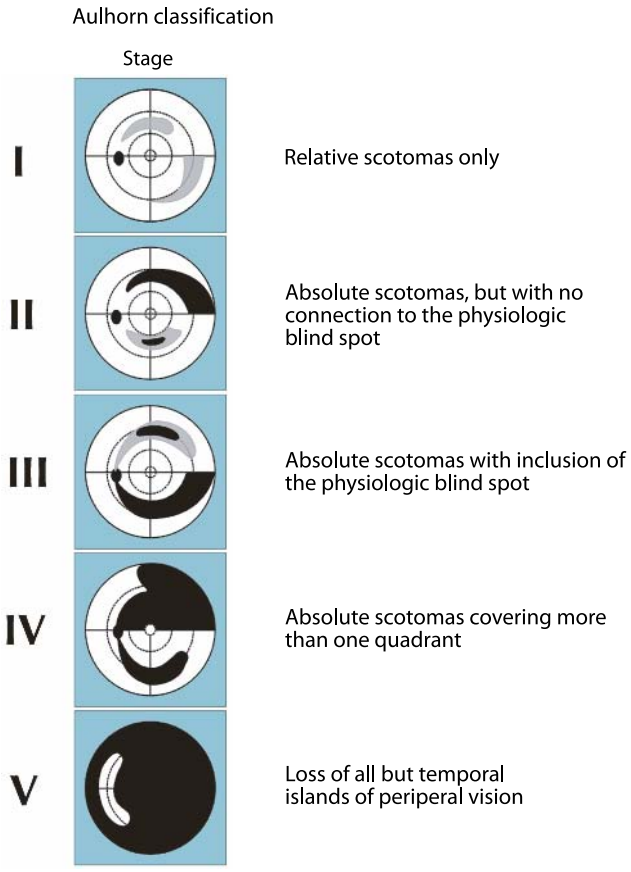


Fig. 4.9. Perimetric staging of glaucomatous nerve fiber bundle defects (modified from Aulhorn et al. 1977)

Typical Perimetric Findings

In general, all of the visual field defects that were detected should be assigned to appropriate classes. This assists in the recording and communication of results on the one hand, and facilitates topographic diagnosis on the other (■ Fig. 4.3).

■ Figure 4.9 and the short compendium of visual field defects is meant to provide a quick and convenient reference source during the day-to-day activity in an ophthalmic practice. Representative visual field findings (each displayed in the left half of the figure) provide starting points for consideration of probable pathogenic mechanisms and differential diagnoses (summarized in the right half).

Since this has primarily to do with recognizing the geometric characteristics of various scotomas, the data on the depth of scotomas have been left out. For the same reason, no numerical data of the "visual field indices" are included. They might be of help in monitoring the course of disease, but are seldom of use in the classification of scotomas. For this purpose, the visual system of the educated physician is much more effective. He/she can use prior experience to recognize typical defects, a task of pattern recognition. The typical perimetric findings are diagrammed schematically with the various scotomas marked in gray.

Conclusion

The physician who can recognize the various forms of perimetric defects and classify them appropriately will benefit from this noninvasive form of diagnostic testing, allowing a specific analysis of the causes and locations of damage to the afferent visual pathway.

Further Reading

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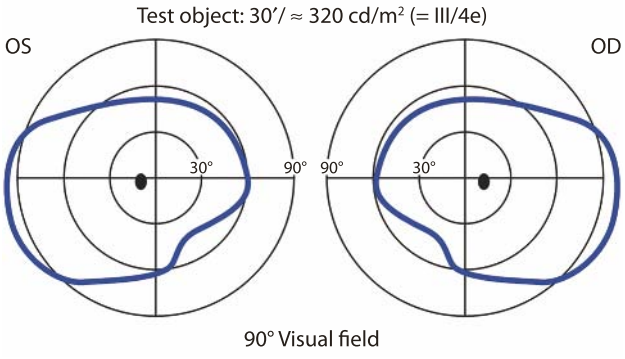
* For those not familiar with the German language, these references are nonetheless useful for their instructive graphics.

Compendium of Visual Field Defects and Their Differential Diagnosis

Normal perimetric findings

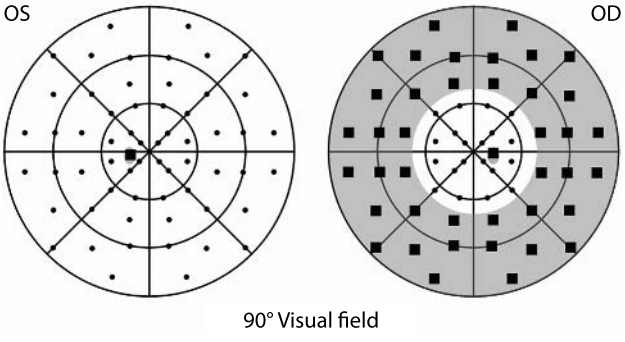


- Normal peripheral isopters plotted with the III/4e test object of the Goldmann perimeter: temporal > 90°, nasal 60°, superior 50°, inferior 60°
- Physiologic blind spot: eccentricity 14°, horizontal diameter 6°, vertical diameter 10°; 2/5 above the horizontal meridian, 3/5 below the horizontal meridian

Visual field defects	Pathogenesis/differential diagnosis

4.1. Loss of peripheral visual field

4.1.1 Concentric constriction



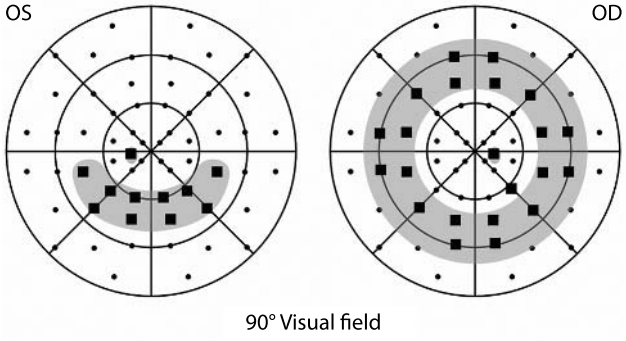
- Fatigue, poor concentration, cannot understand the task of divided attention
- Functional/malingering
- Tapetoretinal degeneration
- Vitamin A deficiency
- Retinoschisis
- Compressive optic neuropathy (see Chap. 8)
- Loss of nasal nerve fibers in glaucoma or optic disc drusen (see Chap. 8)
- Bilateral retrogeniculate damage to the posterior visual pathways (see Chaps. 3 and 12)

Additional testing, when indicated:

- Family history
- Fundoscopy
- Electrophysiology
- Tests of functional disorders, exaggeration and/or malingering (see Chap. 15)
- When indicated: MRI, CT, lab testing

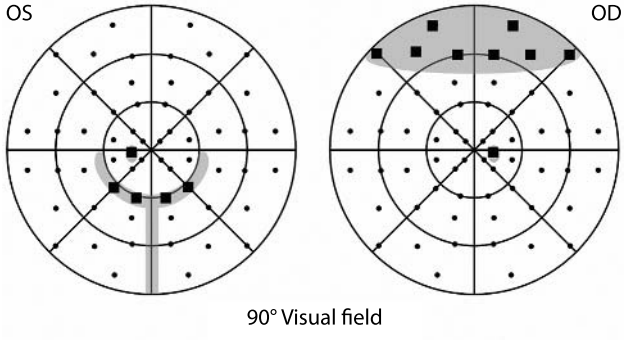
Visual field defects	Pathogenesis/differential diagnosis

4.1.2 Ring scotoma



- Tapetoretinal degeneration
- Artifact: lens rim, lens holder. Check the centering of the perimeter lens
- Be sure to use an age-matched addition when examining the central visual field, i.e., within 30° of the center
- A contact lens may be used if artifacts should persist

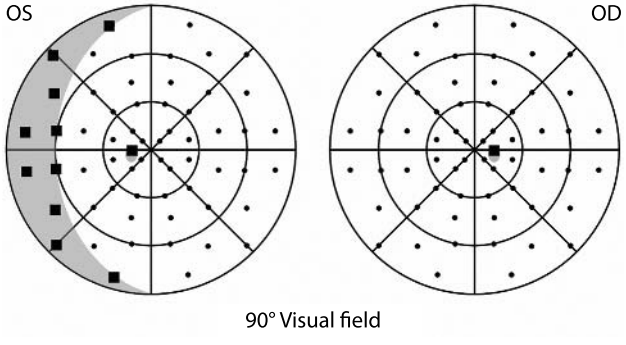
4.1.3 Artifacts



- Obscuration by: (upper) lid, lashes, orbital margin, prominent brow, nose, lens rim, lens holder, eccentric lens
- Fatigue (i.e., when the upper lids descends)

(These problems can be minimized by giving attention to the alignment of the lens and eye, and giving the patient sufficient rest)

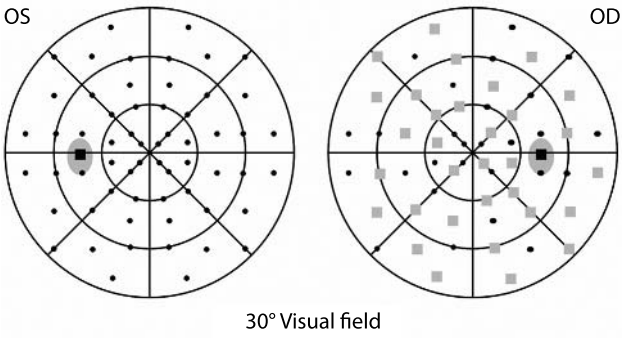
4.1.4 Loss of the monocular temporal crescent



- Contralateral retrogeniculate lesion damaging
  – Meyer's loop in the anterior temporal lobe,
  or
  – the rostral limits of primary visual cortex (in the right hemisphere in this instance),
- Nasal retinoschisis (of the left eye in this example)

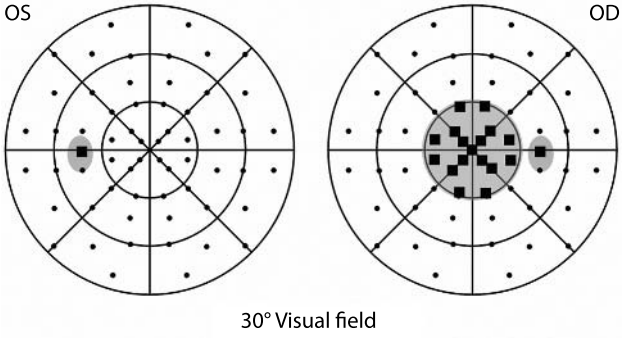
Visual field defects	Pathogenesis/differential diagnosis

4.2 A general reduction of differential luminance sensitivity (DLS)



- Incorrect refraction; avoid using tinted eye glasses; no bi-, tri-, or multifocal lenses; use small rim lenses that are as thin as possible (transposing from plus to minus cylinder can help); correct for presbyopia (see ■ Table 4.3)
- Media opacities
- Fatigue
- (Drug-induced) miosis, e.g., pilocarpine
- Diffuse loss of ganglion cells/partial optic atrophy common, e.g., in early open angle glaucoma and "recovered" optic neuritis

4.3 Central scotoma

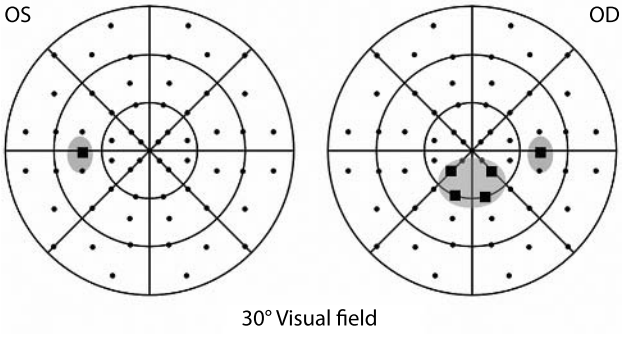


- Central retinopathy
  - Macular degeneration
  - Central areolar choroidal atrophy
  - Cone dystrophy
  - Pigment epitheliopathy
- Optic neuropathy (see Chap. 8)
  - Retrobulbar optic neuritis
  - Toxic or nutritional optic neuropathy
  - Hereditary – familial optic neuropathy
  - Compressive or infiltrative disease

Additional testing, when indicated:

- Family history
- Fundoscopy
- Electrophysiology
- Tests of functional disorders, exaggeration, and/or malingering (see Chap. 15)
- MRI/CT, lab testing

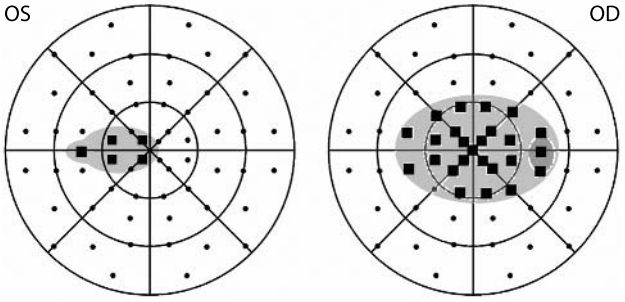
4.4 Paracentral scotoma



- Paramacular retinal/choroidal process
- A small nerve fiber bundle defect
- Atypical retrobulbar optic neuritis
- Artifactual displacement of a central scotoma by eccentric fixation at the scotoma's margin (with corresponding displacement of the physiologic blind spot)

Visual field defects	Pathogenesis/differential diagnosis

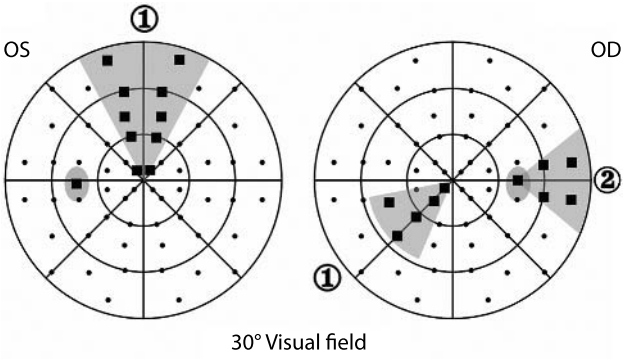
4.5 Cecocentral scotoma
(one that includes both the physiologic blind spot and the papillomacular bundle)



Central retinopathy
- Macular degeneration
- Central areolar choroidal atrophy
- Cone dystrophy
- Pigment epitheliopathy

Optic neuropathy (see Chap. 8)
- Optic nerve pit
- Retrobulbar optic neuritis
- Toxic or nutritional optic neuropathy
- Hereditary – familial optic neuropathy
- Compressive or infiltrative disease

4.6 Sector- and wedge-shaped defects



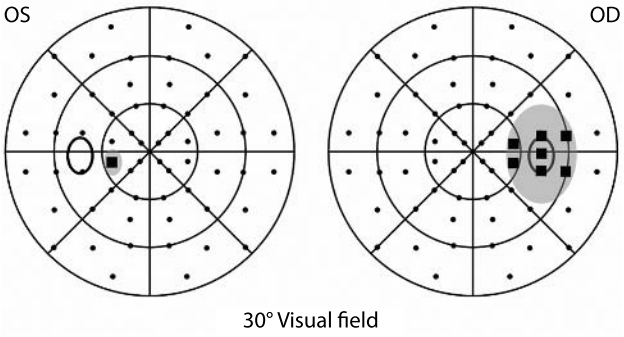
- Disordered choroidal perfusion
  – the apex points to the center of the field (see ①)
- Circumscribed nerve fiber bundle defect in the nasal quadrants
  – the apex points to the physiologic blind spot (see ②)
- (Retro-)geniculate lesions
  – binocular homonymous defects (see 4.9.2.5 in this compendium)

Additional testing, when indicated:
- Fundoscopy
- Fluorescein angiography
- Multifocal ERG
- MRI/CT, lab testing

Visual field defects	Pathogenesis/differential diagnosis

4.7 Pathological changes in the physiologic blind spot

4.7.1 Changes in the size of the blind spot

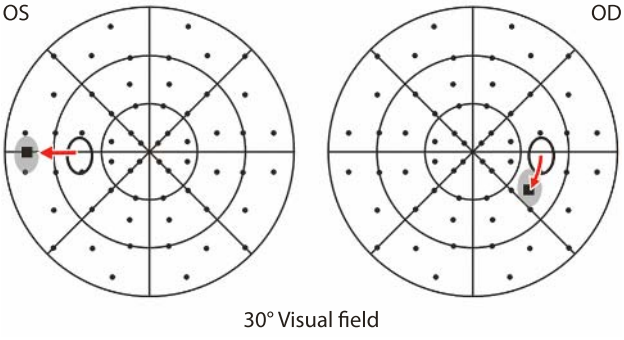


- Magnification:
  - Papilledema
  - Macropapilla, optic disc drusen
  - Coloboma of the optic disc, also known as morning glory syndrome
  - Peripapillary choroidal atrophy or scarring
- Minification:
  - Micropapilla

Additional testing, when indicated:

- Fundoscopy
- Depending on the fundus appearance:
  - Check refraction
  - Measure blood pressure (rule out malignant hypertension with grade IV disc edema)
  - MRI/CT
  - Neurological consultation, lumbar puncture: CSF pressure, CSF lab testing
  - Lab testing

4.7.2 Displacement of the blind spot



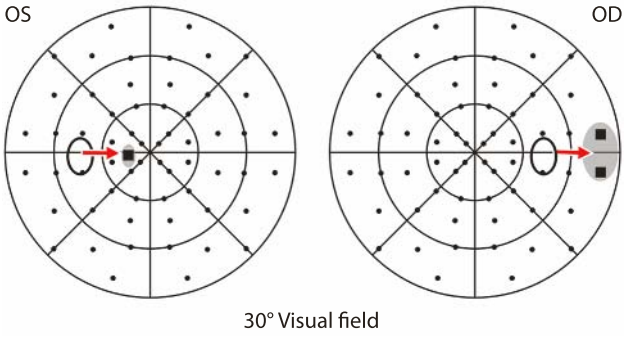
- Strabismus
- Supranuclear disorders of eye movement, e.g., skew deviation, the ocular tilt reaction (see Chap. 11); cyclodeviation, e.g., 4th nerve palsy (see Chap. 10)
- Optic disc ectopia or retinal traction (e.g., retinopathy of prematurity or diabetic retinopathy)
- Artifact

Additional testing, when indicated:

- Fundoscopy (altered optic disc position, tilting of the papillomacular bundle)
- Examination of ocular positions and motility
- MRI/CT, neurological consultation
- ENT consultation

Visual field defects	Pathogenesis/differential diagnosis

4.7.3 Change in size and displacement of the physiologic blind spot

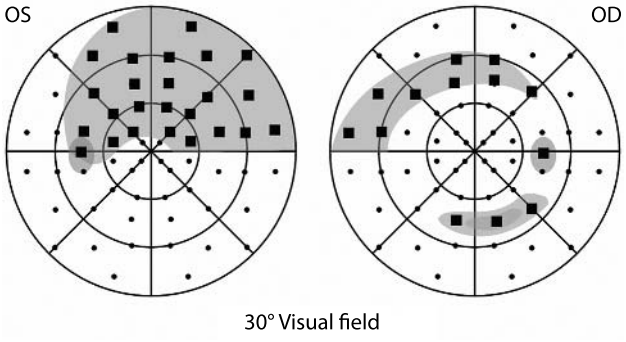


Enlargement and temporal displacement:
- High myopia
- Ocular wall ectasia

Shrinkage and nasal displacement:
- High hyperopia, aphakia

Additional testing, when needed:
- Recheck refraction

4.8. Nerve fiber bundle defects



- Glaucoma
- Anterior ischemic optic neuropathy
- Branch retinal artery occlusion
- Drusen of the optic disc
- Chronic papilledema
- Idiopathic intracranial hypertension (IIH)

(For perimetric staging of glaucomatous nerve fiber bundle defects, see ■ Fig. 4.9)

Visual field defects	Pathogenesis/differential diagnosis

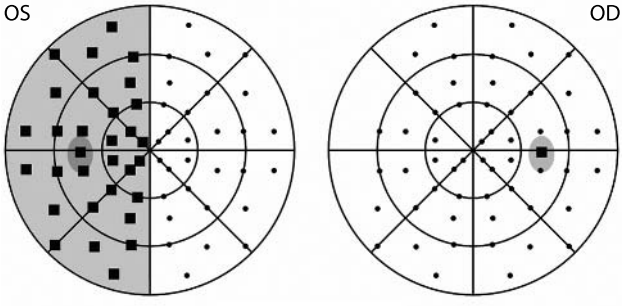
4.9 Hemianopsias

see also Animation 3.2

Note

Every hemianopic visual field defect indicates chiasmal or postchiasmal disease until proven otherwise. When first discovered, such defects require immediate investigation, on a semiemergent basis, by means of CT or MRI imaging

4.9.1 Monocular hemianopsia (rare)



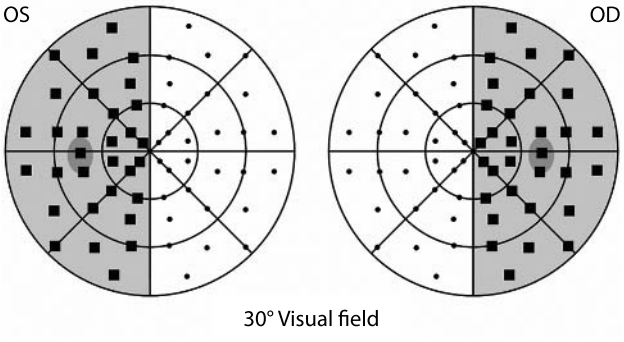
- A prechiasmal process, e.g., optic nerve compression posterior to the optic canal
- Paraneoplastic retinopathy
- Functional disorder, exaggeration, malingering

Additional testing, when indicated:

- Swinging flashlight test
- Color vision testing for hue discrimination and saturation sensitivity (pseudoisochromatic plates, such as the Ishihara series, and/or color sorting tests, such as the Farnsworth D15)
- Fundoscopy of the optic disc and the nerve fiber layer of the retina
- Ocular motility
- Trigeminal nerve function
- MRI/CT
- Electrophysiological testing (VEP)
- Endocrine testing, e.g., for hyperprolactinemia, panhypopituitarism

4.9.2 Binocular hemianopsias

4.9.2.1 Bitemporal hemianopsia



A complete bitemporal hemianopsia, which is relatively uncommon, may cause the so-called hemifield slide phenomenon – see Chaps. 2, 15, and 22.
(Complete bitemporal hemianopsias cause a loss of all binocular vision, with each eye seeing only its nasal hemifield. In the absence of binocular sensory input to fusional vergence movements, the eyes will adopt positions dictated by the mechanics of the ocular and orbital tissues)

Chiasmal disorders – see Chap. 12

- Space-occupying lesions, e.g.:
  - Pituitary adenoma
  - Optic nerve tumor
  - Meningioma
  - Aneurysm

Inflammatory disorders, e.g.:

- Multiple sclerosis, atypical retrobulbar optic neuritis – see Chap. 8
- Wegener's granulomatosis
- Abscess

Vascular disorders, e.g.:

- Pitutiary apoplexy
- Vascular malformations
- Cavernous sinus disease – see Chapter 10
- Radiation neuropathy
- Trauma

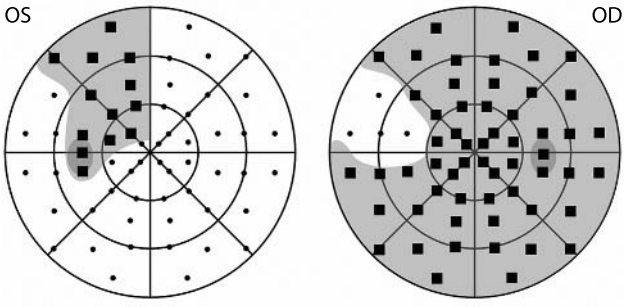
Additional testing, when indicated:

- Please refer to section 4.9.1 in this compendium

Visual field defects	Pathogenesis/differential diagnosis

see also Animation 3.2

4.9.2.2 Anterior junction syndrome – see Chap. 3



30° Visual field

The hemianopic nature of the visual field loss will be evident only when *both* eyes are examined.
The markedly advanced visual loss in the more affected eye can be very severe, allowing only a qualitative perimetric examination in which the chiasmal nature of the damage is hidden, but careful perimetry of the healthier fellow eye will reveal the chiasmal nature of the deficit, reflected in a (temporal) deficit that respects the vertical meridian

- A lesion located at the anterolateral margin of the chiasm, most commonly a meningioma or a supraclinoid aneurysm

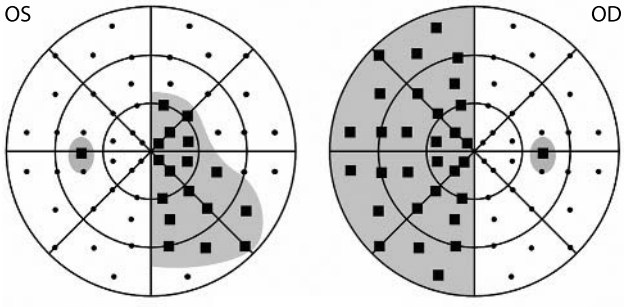
Additional testing, when indicated:

- Please refer to section 4.9.1 in this compendium

! Note

Workup of *any* form of visual loss of uncerain origin must include perimetry of *both* eyes

4.9.2.3 Binasal Hemianopsia



30° Visual field

Binasal defects (respecting the vertical meridian) are very uncommon. Binasal defects are more commonly nerve fiber bundle defects, most often found in primary open angle glaucoma

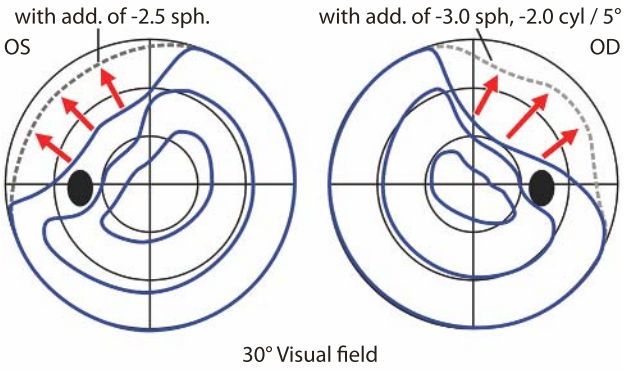
- A parachiasmal lesion: bilateral compression of the lateral aspects of the chiasm by carotid arteries that have calcified walls
- Bilateral papilledema (typically with sector defects in the inferonasal quadrants, and corresponding changes in the optic discs)
- Nerve fiber bundle defects that mimic those of a true hemianopic loss
- Functional disorders – see Chap. 15
- Bilateral retinoschisis in the temporal hemiretinas

Additional testing, when indicated:

- Please refer to section 4.9.1 in this compendium
- Fundoscopy
- MRI/CT scans
- Electrophysiology (mfERG)

Visual field defects	Pathogenesis/differential diagnosis

4.9.2.4 Refraction scotomas with characteristic fundus changes



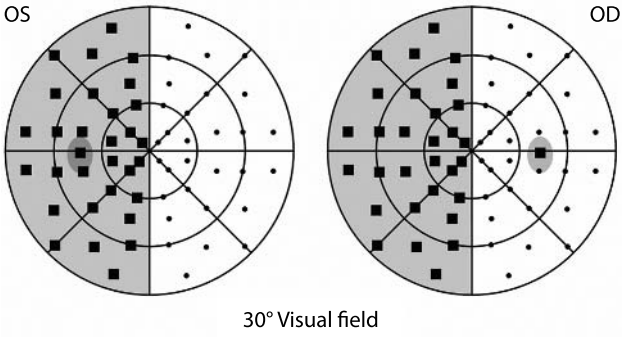
No respect for the vertical meridian, and expansion of the isopters with use of an appropriate lens

- Ocular wall ectasia (usually inferonasal)
- Prominent tilting of the optic disc

Additional testing, when indicated:

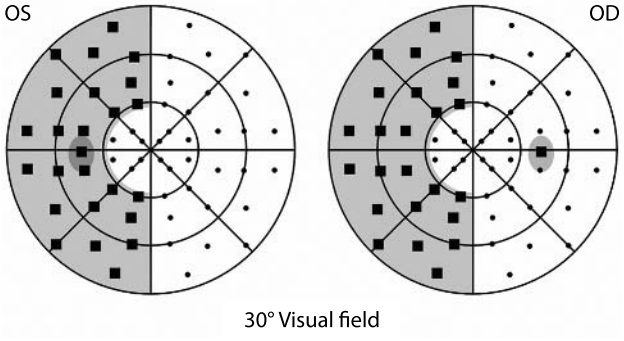
- Fundoscopy
- Streak retinoscopy
- Repeat perimetry with updated refraction

4.9.2.5 Homonymous Hemianopsias



Homonymous hemianopsia to the left with good congruence; no macular sparing causes severe loss of reading ability

- Retrochiasmal lesion in the contralateral hemisphere (e.g., a tract lesion [on the right side], or widespread damage to the retrogeniculate visual system [on the right]
- Vascular disease (in about 75 % of patients)
- Infarction (hemorrhagic or occlusive)
- Arteriovenous malformation or aneurysm
- Space-occupying lesions (in about 15 % of patients)
- Primary brain tumor
- Meningioma
- Metastases
- Inflammation, e.g., multiple sclerosis
- Trauma (up to 2% of patients)

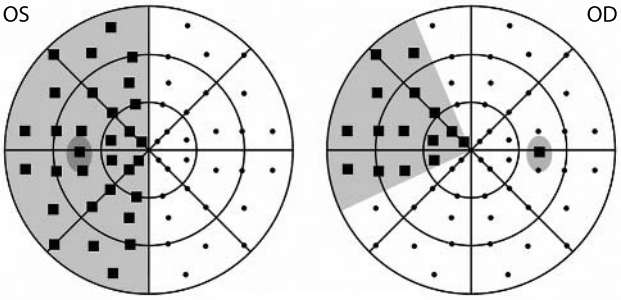
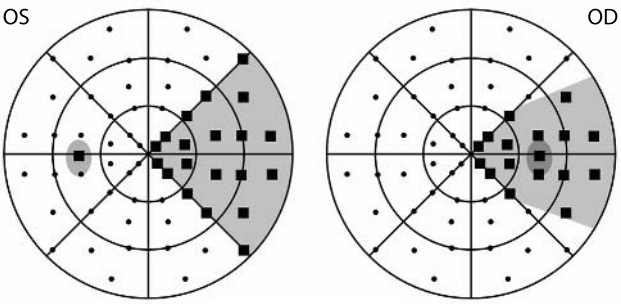
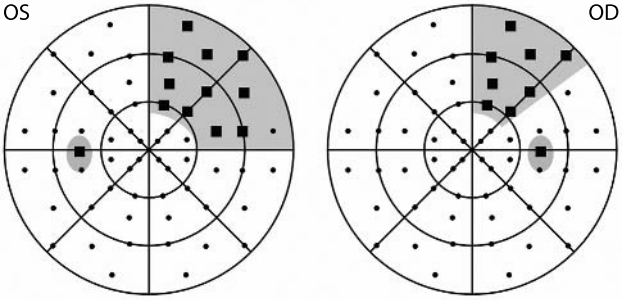


Homonymous hemianopsia to the left with good congruence and distinct sparing of the macular field, allowing retention of fluent reading ability

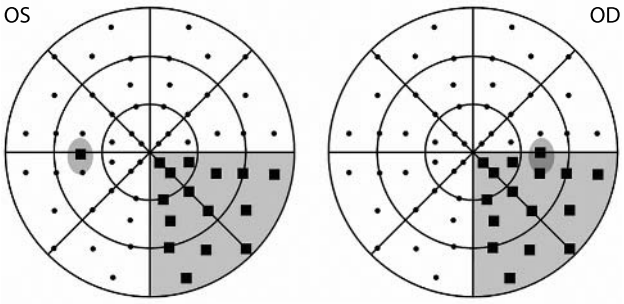
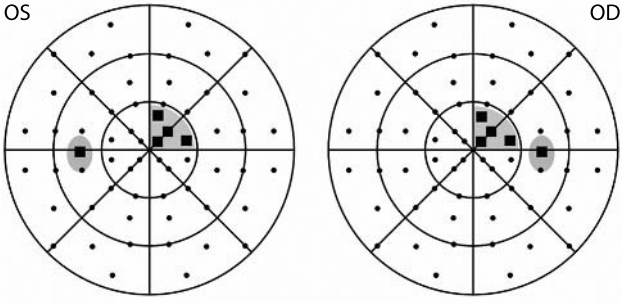
A retrogeniculate lesion of the contralateral hemisphere

Additional testing indicated for homonymous hemianopsias:

- History
- Swinging flashlight test
- Fundoscopy (asymmetric, bilateral optic atrophy caused by tract lesions, see ■ Fig. 8.23)
- MRI, CT, MR-angiography
- Arteriography only when necessary
- Neurological consultation
- Internal medicine consultation

Visual field defects	Pathogenesis/differential diagnosis
 30° Visual field An incomplete homonymous hemianopsia on the left with poor congruence, no macular sparing and consequently poor reading ability	Indicates a retrochiasmal lesion [on the right] This pattern occurs with isolated lesions of the optic tract – such lesions are uncommon, being found in about 4% of cases
 30° Visual field Wedge-shaped, homonymous defect on the right, straddling the horizontal meridian, with some congruence, no macular sparing and consequently poor reading ability	This pattern is associated with lesions of the [left] lateral geniculate body and is quite rare (see ■ Fig. 3.6)
 30° Visual field Homonymous sectors of loss in the right superior quadrant with some congruence, macular sparing and consequent retention of good reading ability	This pattern suggests disease in the [left] temporal lobe – the inferior portions of the optic radiations in the [left] cerebral hemisphere are damaged (see ■ Fig. 3.7c)

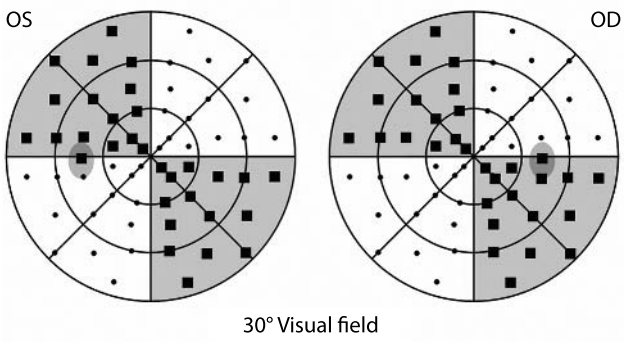
see also Animation 3.3

Visual field defects	Pathogenesis/differential diagnosis
 30° Visual field Sector-shaped, homonymous defects in the right inferior quadrant with good congruence, no macular sparing and poor reading ability	Suggests a parietal lobe lesion [on the left side]; (the superior portions of the [left] optic radiations are damaged – see ■ Fig. 3.7c)
 30° Visual field Small homonymous sectors of loss in the right superior quadrant with very good congruence; in addition it respects both the vertical and horizontal meridians, no macular sparing, poor reading ability	Indicates damage to the visual cortex [on the left side] (caudal portion of the optic radiations damaged – see ■ Fig. 3.7c); respects the border between the superior and inferior quadrants, which are divided by the calcarine fissure; the lesion has damaged the inferior half of the primary visual cortex

see also Animation 3.3

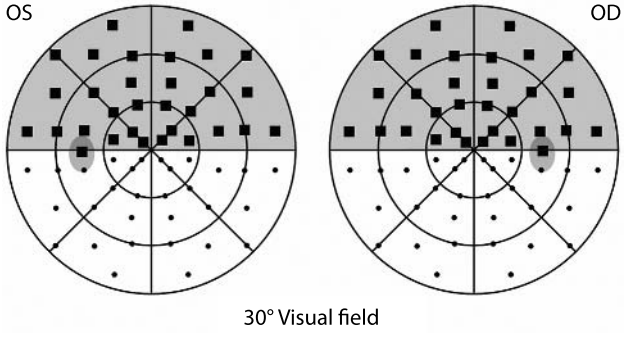
Visual field defects	Pathogenesis/differential diagnosis

4.9.2.6 Bilateral homonymous hemianopsias



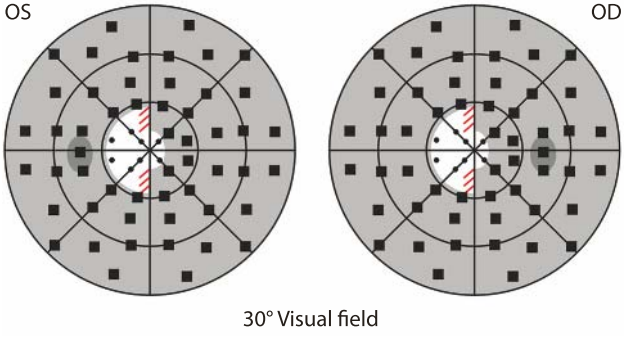
Bilateral homonymous quadrants of loss (so-called checkerboard pattern) with good congruence, no macular sparing and poor reading ability

Usually bilateral occipital lobe infarcts
(In this example the lower half of the visual pathway is damaged on the right side, and the upper half is damaged on the left side)



Bilateral homonymous quadrant defects – altitudinal field loss

Bihemispheric, retrochiasmal lesions (in this example they are both located in the lower half of the retrochiasmal pathway)



"Pseudoconcentric" constriction with apparent congruence, macular sparing, and good reading ability; localized respect of the vertical meridian (see areas hatched in *red*) allows use of the differential diagnosis of a "truly" concentric constriction, as in 4.1.1

Widespread damage to both upper and lower halves of the posterior pathways due to bihemispheric retrochiasmal disease

Chapter 5

Diagnosis of Pupillary Disorders

H. Wilhelm and B. Wilhelm

Pupillary testing serves two purposes, first, to find disorders of pupillary function itself, and second, to detect disorders of the afferent visual system and the autonomic innervation of the eye. A systematic approach will help significantly with interpretation of the findings. The examination should be done in a logical order, since the pupillary system responds in a logically predictable way. Tests that yield no useful information can only create confusion.

Anatomic and Physiologic Fundamentals of the Pupillary System

There is a great deal of useful information in the anatomy and physiologic responses of the pupillary system, information that the clinician can put to immediate good use. Three aspects of pupillary behavior are of particular relevance during a clinical examination:

1. The size and speed of pupillary constriction in response to a light stimulus of medium strength are proportional to the logarithm of the luminance intensity of the stimulating light. This being the case, pupillary responses can be used as a test of the eye's sensitivity to light. This is the basis for the interocular comparisons made during the swinging flashlight test as described in Chap. 2.
2. Normal pupillary reactions are highly variable and are influenced by many variables (status of accommodation, emotions, vigilance, drug effects). This variance is both inter- and intraindividual, which diminishes the value of individual observations and requires multiple repetitions of a test, before a pathological finding can be confirmed.
3. The pupillomotor centers in the pretectal midbrain – a region of nuclear centers anteroventral to the quadrigeminal plate – receives neural signals evoked by retinal illumination and transmitted by way of the optic tract (■ Fig. 5.1). Pupillomotor afferents are not separated by eyes, but rather by visual hemifields. Each side of the pretectum in turn sends signals via multisynaptic connections to both sides of the Edinger-Westphal nuclei. Neurons with their somas in these nuclei send their

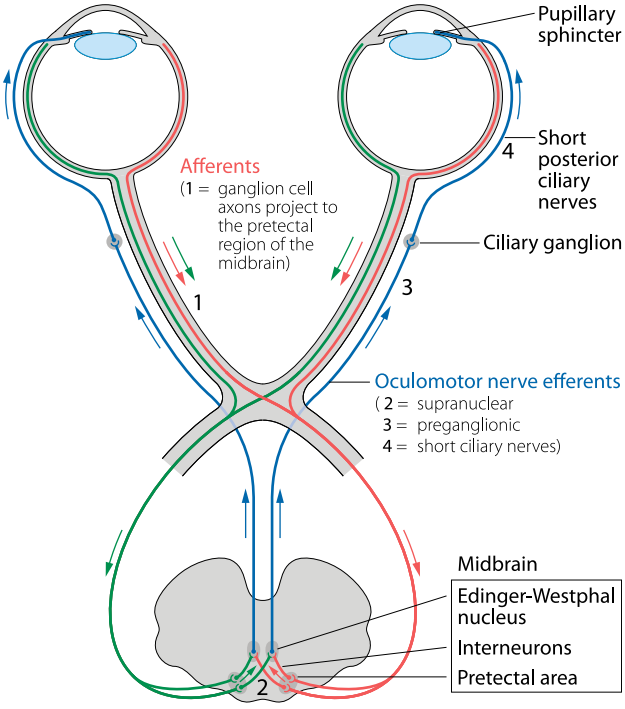
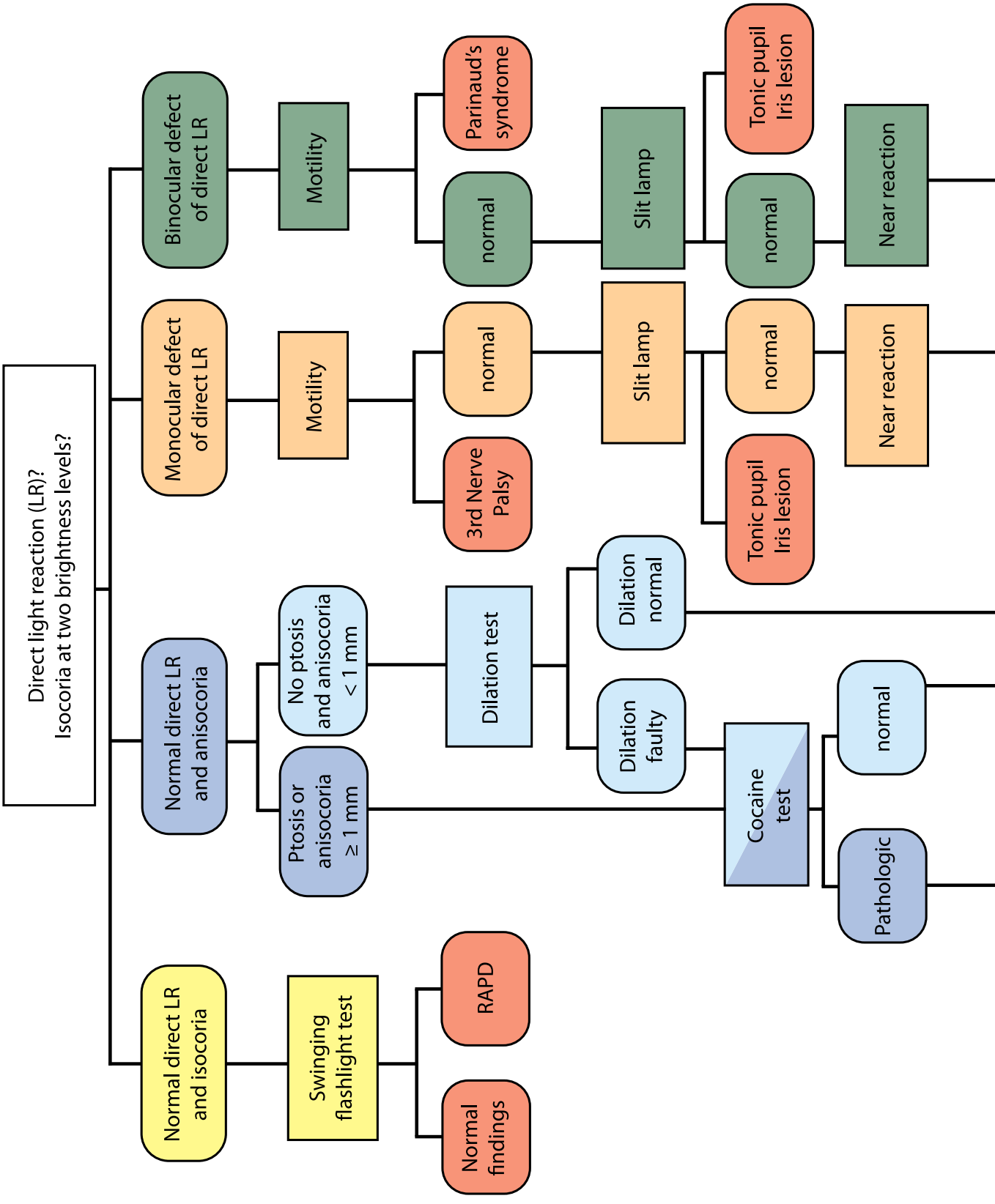
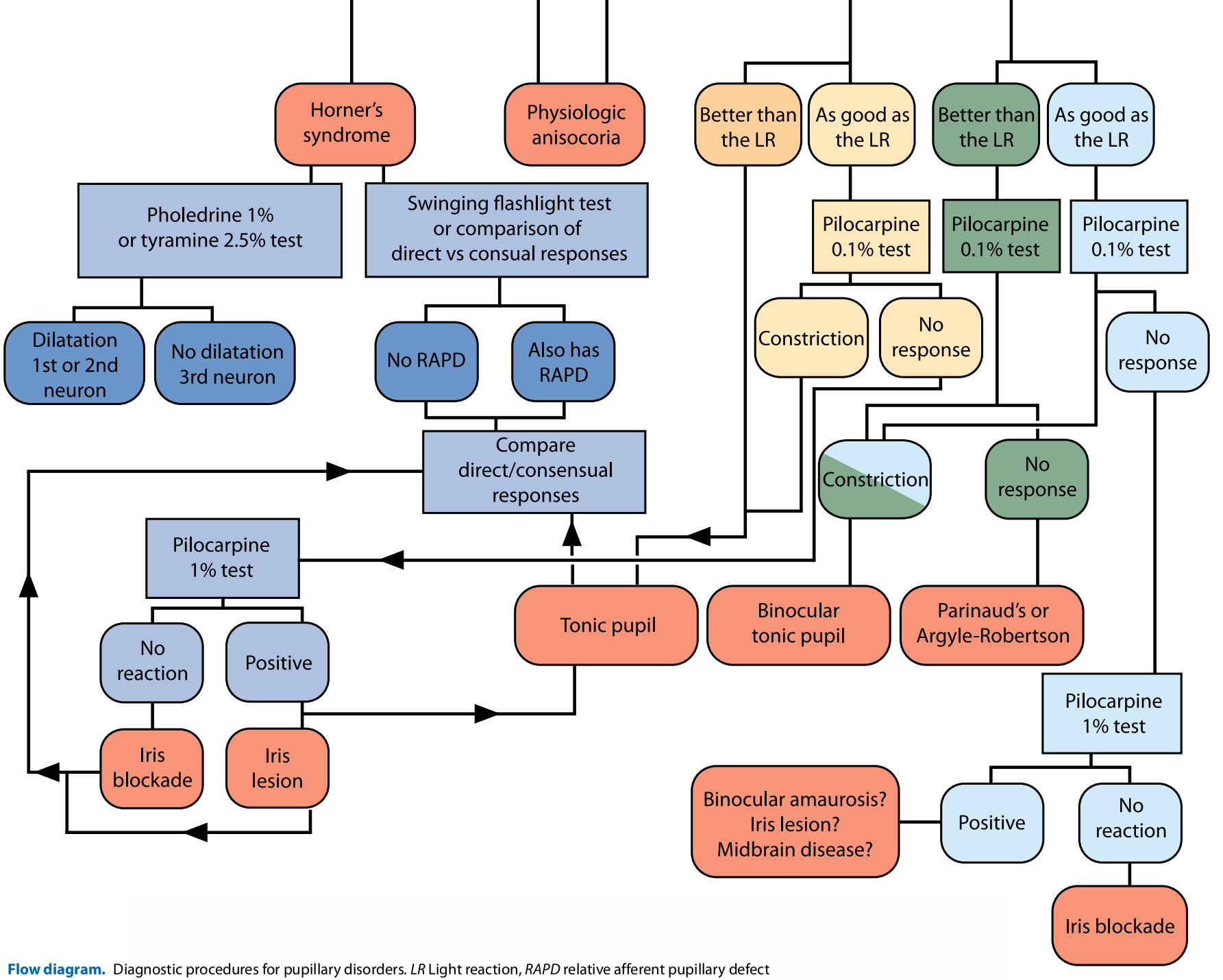


Fig. 5.1. Schematic overview of the anatomy of the pupillary light reflex arc. By way of the optic tract the afferent path (*1*) of the pupillary system projects to the dorsal midbrain (pretectum, *2*). From there, the signal is carried to the Edinger-Westphal subnucleus in the nuclear complex of the oculomotor (third) cranial nerve. The oculomotor nerve innervates the ciliary ganglion (*3*), from which the short posterior ciliary nerves arise and enter the eye to innervate the pupillary sphincter (*4*). Not to be overlooked are afferents in this reflex system that arise in the visual cortex and project to the pretectal region, providing another input pathway that participates in the reflex process


Direct light reaction (LR)?
Isocoria at two brightness levels?
Binocular defect of direct LR
Motility
Parinaud's syndrome
normal
Slit lamp
Tonic pupil Iris lesion
normal
Near reaction
Monocular defect of direct LR
Motility
normal
3rd Nerve Palsy
Slit lamp
normal
Tonic pupil Iris lesion
Near reaction
Normal direct LR and anisocoria
No ptosis and anisocoria < 1 mm
Dilation test
Dilation normal
Dilation faulty
Ptosis or anisocoria ≥ 1 mm
Cocaine test
normal
Pathologic
Normal direct LR and isocoria
Swinging flashlight test
RAPD
Normal findings



Flow diagram. Diagnostic procedures for pupillary disorders. *LR* Light reaction, *RAPD* relative afferent pupillary defect

axons by way of the third cranial nerve to the ipsilateral ciliary ganglion from where postganglionic parasympathetic fibers innervate the eye via the short posterior ciliary nerves, terminating at the pupillary sphincter. This anatomically bilateral sharing of neural input has the important consequence that damage to the afferent visual pathways that lead to the Edinger-Westphal nucleus *cannot cause an anisocoria*. Thus, anisocoria is never a sign of an afferent disturbance, but is always a sign of an efferent pupillary disorder. This is the physiologic foundation for the tests to be described in the following sections of this chapter.

What Is Needed For Pupillary Testing?

Pupillary testing requires two bright lights (e.g., an indirect ophthalmoscope and a bright flashlight), a pocket gauge for measuring pupillary diameters, neutral density filters, a slit lamp, a topical solution of 5% cocaine, occasionally a 1% solution of hydroxyamphetamine (where available), pilocarpine 0.1% and 1.0%, and phenylephrine 2.5% eye drops.

Pearl

For presbyopic examiners, a generous near correction is needed for adequate study of pupillary sizes, shapes, and movements. Pupillary examinations are usually best done in a dimly illuminated, nearly dark room (see below), which makes proper correction of the examiner's refractive errors particularly important.

Systematic Examination of the Pupils

First step: Confirm that the pupils respond to light. Only in the dark can the pupils really show how well they can react, so be sure that the room light is as dim as convenience will allow. The patient should be asked to look into the distance, to limit intrusion by the miosis of the near reflex. Using a strong light source (such as an indirect ophthalmoscope) stimulate both eyes simultaneously. If both pupils visibly and symmetrically constrict, go to the second step.

If one or both pupils do not appear to react, a pathological state in need further examination has been found (go to the fourth step).

Second step: Compare the pupillary diameters to one another. Examination and interocular comparison of the pupillary diameters determines whether the autonomic (efferent) innervation of the eye is intact. If there is an anisocoria, repeat testing of both pupils' responses to a strong, binocular light stimulus.

Pearl

These two steps can be combined. Illuminate both eyes from a position below the visual axis and then slowly bring the light source closer to the eyes. Determine whether the pupils are symmetrical in size and whether both constrict equally.

Third step: Do the swinging flashlight test. This step compares the afferent pupillary responses of one eye to the other. (The swinging flashlight test is described in detail in Chap. 2).

When a pupil is poorly reactive or does not react to a light stimulus, the swinging flashlight test cannot be done in the usual way since the test requires that both pupils react equally to light. Moreover, if there is an anisocoria, the requirements for this test are somewhat different. Experience has found that when there is an interocular difference of 0.5 mm or more in pupillary diameter, the test is best done by judging the movements of the pupil that has the better light reaction, comparing its direct and consensual responses. This method is more completely described in Chap. 2.

Anisocorias of 0.3 mm or less are not usually visible. If normal responses have been found up to this point, the test is concluded. It should be recorded as, "Pupils sizes and light responses are equal; there is no relative afferent pupillary defect."

Fourth step: Examination of pathological findings. After completion of the first three steps, the following pathological states are possible:

1. A relative afferent pupillary defect (RAPD)
2. An anisocoria with normal responses to light in both eyes
3. A monocular or bilateral deficit in light responses

Further Testing When Pupillary Signs Are Abnormal

Relative Afferent Pupillary Defect

When an RAPD is found, the cause must be identified. This process is described in some detail in Chap. 2. If the cause cannot be found, perimetric examination of both eyes is necessary.

Anisocoria with Bilaterally Normal Pupillary Reactions to Light

Dilation Test

The dilation test uses a comparison of the speed of pupillary dilation of both eyes after extinguishing a bright light stimulus. It determines whether there is evidence of a problem with sympathetic innervation of the pupil(s). A prob-

Video 5.1

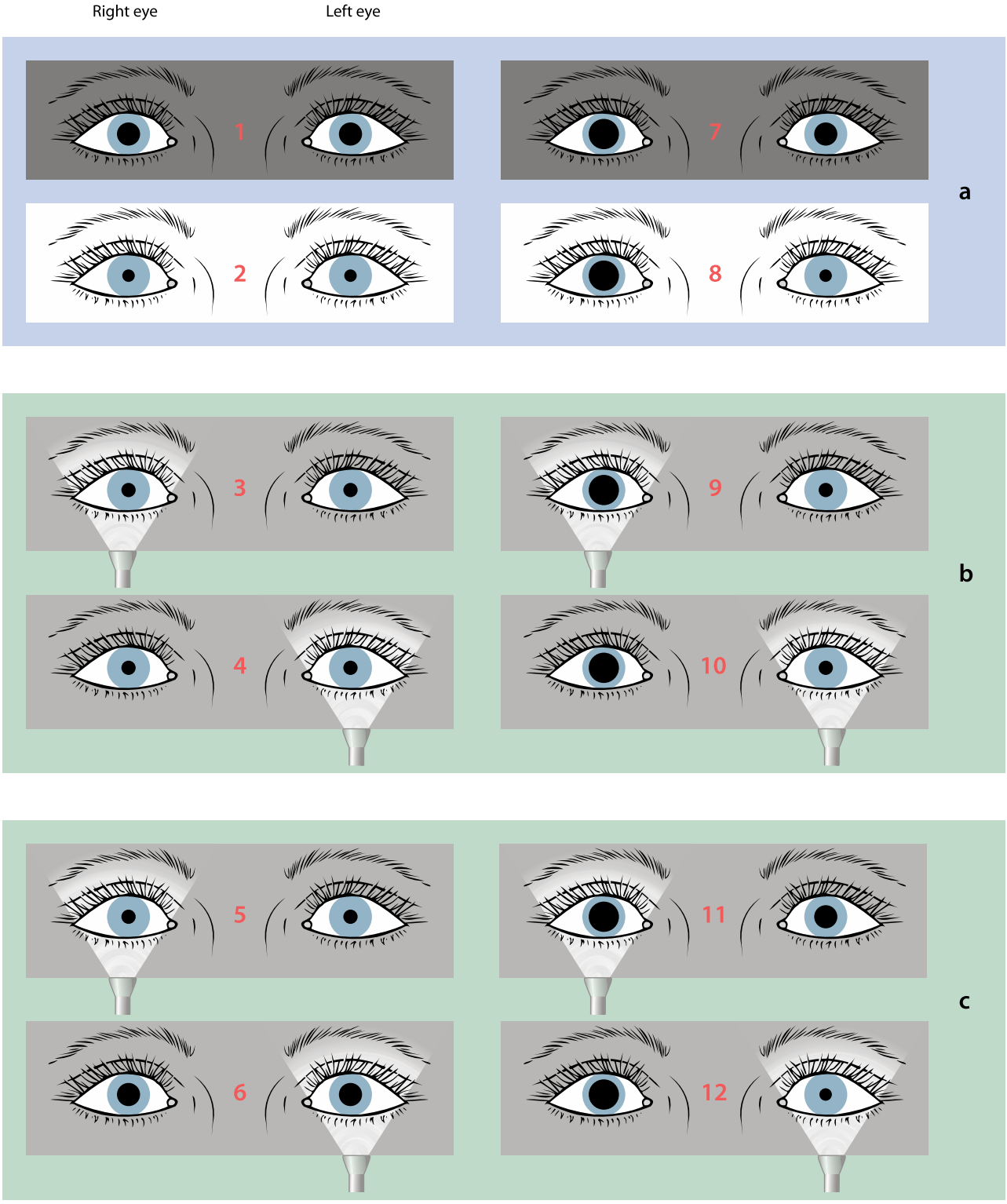


Fig. 5.2. Typical responses of the pupils in the normal state and in the classical pupillary disorders during routine examination. **a** Testing of anisocoria and the pupillary light response. **b** Responses to the swinging flashlight test with normal afferent function. **c** Responses found in monocular disorders of the afferent portion of the reflex arc. *1* Inspection in the dark; *2* inspection with lights on: no anisocoria, and with either normal responses or signs of an afferent defect; *3*, *4* light reactions for the interocular comparisons during the swinging flashlight test with normal responses and no relative afferent pupillary defect (RAPD); *5*, *6* left RAPD; *7–12*: pupillary light responses in the case of a widely dilated pupil in the right eye that does not respond to light; *9*, *10* no RAPD; *11*, *12* in the presence of an RAPD on the right

lem is that the test is done in a darkened room. Ideally, one should use an infrared video system to examine pupillary movements in the dark, i.e., after turning the light stimulus off. A practical alternative is to use a separate, weak light source to illuminate both eyes at a tangential angle from below, so that both pupils are visible and a minimum area of retina is being illuminated in each eye. It is best not to look at the eye with the brighter stimulus, since this causes light adaptation of the examiner's eyes, making it difficult to see the dimly illuminated pupil.

When the pupils dilate well and with no speed difference between them, the anisocoria is likely to be physiologic. Physiologic anisocoria of greater than 1 mm is very uncommon, so when the difference is greater than 1 mm, use of the cocaine test is necessary (see below). Also, when the smaller pupil dilates more poorly, the cocaine test is likewise indicated.

Video 5.2

Video 5.3

! Note

Observation of the pupils in the dark with infrared light is simpler and more effective than are examinations done under dimly illuminated conditions. Infrared video recording is now easy to implement. Video camcorders commonly have a "night" or "zero lux" setting, which is a form of infrared video recording. The barrier filter of the camera can be removed, and an infrared light source turned on. Such devices are reasonably inexpensive, making their use for pupillary testing very attractive.

Cocaine and Hydroxyamphetamine Tests

The cocaine test is indicated in three situations:

1. For anisocoria greater than 1 mm and normal pupillary light reactions
2. For slower dilation of the smaller pupil
3. For ptosis ipsilateral to the smaller pupil (suspected Horner's syndrome)

Cocaine retards the reuptake and inactivation of noradrenalin within the synaptic cleft. Thus, it is an indirect sympathomimetic. When sympathetic innervation is intact, there is a constant rate of release of noradrenalin into the synapse, and cocaine blocks its reuptake, causing an accumulation of the neurotransmitter, and resulting in pupillary dilation. If the anisocoria is physiologic, the smaller pupil dilates more than does the larger pupil, reducing the anisocoria.

Drops of 5% cocaine are instilled in both eyes (all pharmacologic pupil testing should be done symmetrically, comparing one eye to the other). This preparation is usually available at hospital pharmacies. If there is any uncertainty about the completeness of an application to either eye, the drop should be immediately repeated. When testing infants and small children, use of a 2.5% solution of cocaine is recommended. The diameters of both pupils are measured before and 1 h after instillation of the drops, using the same levels of illumination for both measures. It is usually sufficient to measure the pupils' diameters with a pocket card that has semicircles of various diameters arrayed along one margin. If greater precision is desired, the measurements should be done with photography.

Pearl

If 1 h after cocaine instillation there remains a difference between the pupillary sizes of 1 mm or more, this should be accepted as reasonable proof of Horner's syndrome (■ Fig. 5.3). If the anisocoria is less than 0.3 mm, it is most likely physiologic. However, one should take into account that 5% cocaine produces an average dilation of 2.1 mm in normal pupils and 0.5 mm in pupils affected by Horner's syndrome. Only 3% of Horner's-affected pupils respond with a dilation of more than 1 mm, so when cocaine produces a dilation of 1.5 mm or more, Horner's syndrome can be effectively ruled out.

Thus, cocaine testing clearly differentiates physiologic anisocoria from Horner's syndrome. ■ Table 5.1 lists the limiting values. In cases of doubtful results, the test should be repeated. In the United States, where random testing by employers is common, subjects tested with cocaine should be given certificates indicating that they have been exposed to cocaine as a medical testing agent. The effect of topical administration of a 5% solution of cocaine to the eye can be detected in urine samples for several days.

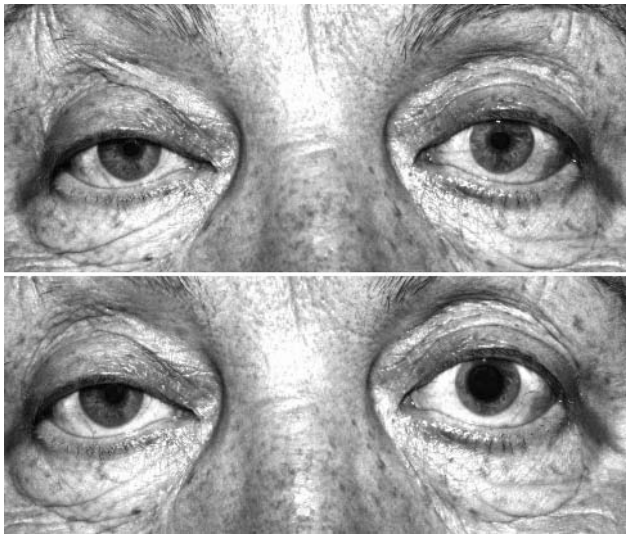


Fig. 5.3. Horner's syndrome (*right side*) before and after cocaine test

Table 5.1. Cocaine testing for Horner's syndrome

	Anisocoria 1 h after topical instillation of 5% cocaine solution	The effect of 5% cocaine eye drops on the smaller pupil
Horner's syndrome	≥1 mm	<0.5 mm
No Horner's syndrome	≤0.3 mm	≥1.5 mm
Horner's syndrome suspected	0.4–0.9 mm	Borderline values with no persuasive evidence of Horner's syndrome

Other indirect adrenergic agents, such as 1% hydroxyamphetamine or 2.5% tyramine, have their effect by stimulating the release of noradrenalin into the synaptic cleft at the terminus of the end neuron of the sympathetic chain. These drugs have their adrenergic effect only if the end neuron is intact and functioning. If the terminal neuron has died, its transmitter production is gone with it. The procedure is the same as with the cocaine test, except that the pupils are measured 45 min after the administration of the drops. The mydriatic effect matches that effect found with cocaine testing. If the unaffected pupil dilates well and the affected pupil dilates by 0.5 mm or less, the loss of adrenergic function of the affected pupil can be attributed with confidence to damage to the third (terminal) neuron of the sympathetic pathway, i.e., at or above the ganglion cervicale superius of the sympathetic chain.

Pearl

If the affected pupil dilates as well or better than its contralateral partner, the site of damage lies somewhere below the level of the ganglion cervicale superius, i.e., in the first- or second-order neurons of the sympathetic pathway.

Lower concentrations of phenylephrine (about 2%) are well suited to the pharmacologic detection of weakened pupillary dilators. Among infants, one often finds an anisocoria with normal pupillary light reactions and no ptosis that persists after instillation of topical cocaine. If the anisocoria persists after instillation of 2.5% solution of phenylephrine, it can be concluded that the dilator of the smaller pupil is probably hypoplastic. This is a benign disorder not associated with any other abnormalities of anterior segment development, and it commonly normalizes with the passage of time.

Unilateral or Bilateral Disturbances of Pupillary Light Reactions

Testing the Near Reaction

The near reaction must be tested when there is a unilateral or bilateral abnormality of the pupillary light reaction.

Pearl

It should be kept in mind that the pupils of children and younger adolescents frequently do not react until the distance between eye and object of regard is very short (about 10 cm).

There are no documented reports of an isolated loss of the pupillary near reaction. An exception may be the pupillary disturbances found associated with botulism or diphtheria, in which accommodation and the pupillary near response are significantly more affected than is the light reaction. Nonetheless, the pupillary light response is not normal in this setting.

When testing the pupillary near reaction, the level of illumination should be bright enough that the pupils can be easily seen, and an object with fine surface detail (to encourage accommodation) is slowly brought toward the eye.

Definition

Pupillary testing results most often show that the light and near reactions of the pupil are equally impaired or preserved. In some cases, the near response will be found better preserved than the reaction to light. The latter state is called **light-near dissociation**.

Oculomotor Testing

A monocular defect in the light response of the pupil raises the question of a third nerve paresis (see Chap. 10), while bilateral deficits can be associated with vertical gaze palsies, such as in Parinaud's syndrome (see Chap. 11).

Slit-Lamp Examination

The slit lamp allows close examination of the anatomy of the pupil and iris, particularly with respect to evidence of sphincter atrophy or traumatic disruption. The examiner should note whether the sphincter shows spontaneous movements, whether a strong light stimulus produces a correspondingly large response of contraction, whether some segments of the sphincter move more strongly than

do others, and whether spontaneous, pathological vermiform movements are present. If the pupil does not appear to respond to a light stimulus, its near response can be tested at the slit lamp. In addition, segmental pareses (causing odd-shaped pupils) and vermiform movements (tonic pupils) are easily seen through the slit-lamp instrument. The slow redilation of a constricted pupil seen at the slit lamp also helps to confirm the tonic behavior of an Adie's pupil.

Testing with Pilocarpine 1% and 0.1%

Testing with weak (0.1%) pilocarpine is useful when the diagnosis of a tonic pupil is suspected but not clearly confirmed at the slit lamp. The tonic pupil has a characteristic denervation hypersensitivity to a cholinergic stimulus, which can be associated with Adie's syndrome or a paresis of the oculomotor nerve. Use of the weaker concentration of pilocarpine should always be done first if there appears to be an absolute pupillary paralysis (no response to either light stimulation or prolonged accommodative effort). An immobile, circular pupil at a mid-dilation position is often present in the early stages of Adie's tonic pupillary syndrome.

Testing with weak pilocarpine can be affected by the state of the corneal surface permeability. All testing that can be expected to change the permeability (e.g., tonometry) should be done after the weak pilocarpine test.

Pearl

Testing with the higher (1%) concentration of pilocarpine is indicated when light, maximal accommodative effort, or weak pilocarpine will not cause the pupil to constrict. If the higher concentration of pilocarpine fails to constrict the pupil, there is a problem within the iris/pupil itself. If an anticholinergic drug (such as atropine or scopolamine) has produced a pharmacologic dilation, the test with 1% pilocarpine is the one reliable way of proving a drug-induced mydriasis. The test is considered positive if the pupil fails to react at all, or responds only minimally. In cases of doubt, the test can be repeated in the contralateral eye to help clarify the diagnosis. In cases of oculomotor paralysis, for example, 1% pilocarpine will reliably cause pupillary miosis, assuming that there is no prior history of injury or surgical manipulation of the iris.

Common Pupillary Syndromes and Their Diagnoses

Horner's Syndrome

Definition

Horner's syndrome is a monocular loss of sympathetic innervation to the eye. This causes a loss of function in all of the ocular structures that are sympathetically controlled. The pupil is smaller, but the light reaction remains normal. In 90% of cases, there is a ptosis of the upper lid, caused by paresis of Müller's smooth muscle within the palpebral levator muscle complex. At the same time there is a small elevation of the lower lid as well, since the lower lid retractors are also sympathetically innervated. The narrowing of the palpebral fissure causes the appearance described as "apparent enophthalmos." If the site of damage to the sympathetic path lies proximal to the branching of the fibers that mediate sweating and temperature regulation in the face, these functions will also be impaired. The face will appear flushed on one side, with a sharp dividing line that runs precisely along the sagittal midline.

If it is available, instillation of hydroxyamphetamine can help to localize the site of damage more precisely (see above). This allows for a more systematic approach to the diagnosis. ■ Figure 5.4 diagrams the complex pathway of sympathetic innervation of the eye. The principle of further testing of Horner's syndrome is to look for findings in anatomically neighboring structures that help to fix the localization and pathogenesis of the damage. Neurological deficits in brainstem function that accompany Horner's syndrome suggest a proximal site of damage, while symptoms or signs related to the brachial plexus or thorax indicate a more distal site of damage. Brainstem disease can also lead to abnormal eye movements, changes in the vestibulo-ocular reflex, and nystagmus. The regions implicated by such findings should be imaged by CT or MRI scanning. Referral to an appropriate service for investigation of suspected mediastinal or cervical disease may be indicated, but the ophthalmologist should first inspect and palpate the soft tissues of the neck to rule out a large goiter, which is usually easy to detect.

Fig. 5.4. Course of the peripheral sympathetic supply to the pupil and to Müller's muscle. The most common lesions affecting these regions are *1* brainstem stroke, *2* syringomyelia, *3* prolapsed intervertebral disc, *4* thoracic outlet syndrome, *5* mediastinal tumors, *6* Goître, *7* dissecting carotid aneurysm, *8* carcinoma of the paranasal sinuses, *9* tumors of the cavernous sinus, and *10* cluster headaches

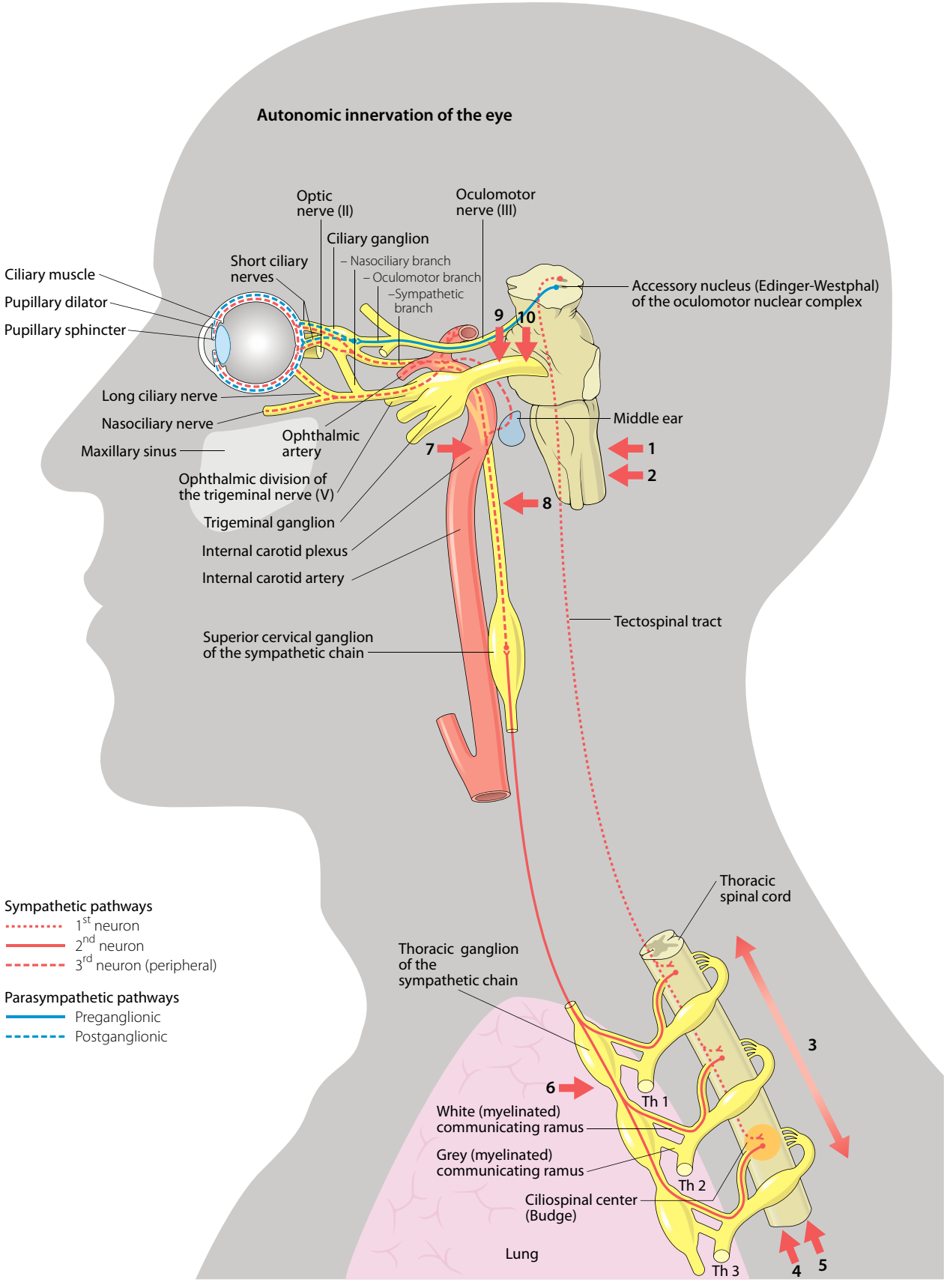

Autonomic innervation of the eye
Optic nerve (II)
Oculomotor nerve (III)
Ciliary ganglion
Short ciliary nerves
– Nasociliary branch
– Oculomotor branch
–Sympathetic branch
Ciliary muscle
Pupillary dilator
Pupillary sphincter
Accessory nucleus (Edinger-Westphal) of the oculomotor nuclear complex
9
10
Long ciliary nerve
Nasociliary nerve
Maxillary sinus
Ophthalmic artery
Middle ear
7
1
2
8
Ophthalmic division of the trigeminal nerve (V)
Trigeminal ganglion
Internal carotid plexus
Internal carotid artery
Tectospinal tract
Superior cervical ganglion of the sympathetic chain
Thoracic spinal cord
Thoracic ganglion of the sympathetic chain
3
6
Th 1
White (myelinated) communicating ramus
Grey (myelinated) communicating ramus
Th 2
Ciliospinal center (Budge)
Lung
Th 3
4
5
Sympathetic pathways
1st neuron
2nd neuron
3rd neuron (peripheral)
Parasympathetic pathways
Preganglionic
Postganglionic

Fig. 5.4.

Table 5.2. Recommended workup for cases of Horner's syndrome

When preganglionic pharmacologic testing is positive: • Evaluation by an internist and a neurologist, and neuroradiologic evaluation for cases in which there are additional signs and symptoms
When postganglionic pharmacologic testing is positive: • If the problem is isolated and not acute, seek a history of cluster headaches or migraine • When additional cranial nerves are involved, or the problem is acute, refer for MRI or CT
When the problem is congenital or infantile: • Rule out neuroblastoma

It is possible for malignant disorders to present initially as Horner's syndrome, but the usual causes are much more commonly benign or indeterminate. It is advisable to limit the extent of diagnostic testing and to keep the patient under observation when the initial steps in the evaluation have failed to detect a cause (■ Table 5.2). Monitoring of the patient's findings for changes in signs or the onset of additional symptoms is recommended. Any significant change should be cause for a renewed attempt at localizing the site of damage, since there are disorders that can respond to interventional treatment.

! Note

It is important, however, to keep in mind that acute and painful onset of Horner's syndrome is the classic presentation of a carotid artery dissection of the carotid artery, which can occur spontaneously or after minor trauma. It has been associated at times with chiropractic manipulation of the neck. The risk of stroke in these patients is very high, and correct management involves immediate anticoagulation. Patients with this syndrome are commonly tall and slender people, and there is an association with connective tissue disorders like Ehlers-Danlos syndrome.

A singular form of Horner's syndrome is the congenital or infantile onset. Hydroxyamphetamine testing is not usually helpful, since trans-synaptic degeneration can affect the third-order neuron, even though the lesion may lie upstream in the first or second-order neurons. In such cases, the drug may not cause pupillary dilation. In addition, there is usually a visible heterochromia iridis, since development of the iris pigmentation requires an intact sympathetic innervation. The affected eye appears bluer. In addition, in adults with Horner's syndrome, depigmentation of the iris can occur over a period of years.

● Pearl

The cause of Horner's syndrome in children is most commonly birth trauma. Another less common but more dangerous cause is neuroblastoma, which should be specifically ruled out.

Tonic Pupil Syndrome

: Definition

Tonic pupil syndrome is a usually monocular loss of parasympathetic innervation of the eye. The site of damage is at the ciliary ganglion or in the short posterior ciliary nerves.

The tonic pupil presents a frequent diagnostic problem, since it is common and does not have a single, typical appearance. It commonly leads to extensive diagnostic testing that fails to identify the source and causes the patient considerable anxiety. Once the diagnosis has been correctly established, further testing is only occasionally necessary.

Most commonly, the affected patients are women between 30 and 40 years of age. However, it can occur at any age. In a few cases, the cause can be established, or at least confidently suspected, e.g., after orbital trauma, extensive panretinal photocoagulation, outbreaks of varicella zoster, orbital ischemia with active giant cell arteritis, and only rarely associated with a malignancy and a suspected paraneoplastic syndrome.

Typically, though, the tonic pupil is harmless. In most instances it is idiopathic (has no identifiable cause). It is frequently associated with a loss of deep tendon reflexes (Adie-Holmes' syndrome), or less commonly with sudomotor disturbances (Ross syndrome) or with vascular disease. None of these idiopathic types of tonic pupil is so severe as to cause the patient significant loss of visual function.

● Pearl

Presentation of an acutely tonic pupil in patients over 50 years of age should lead to testing of the erythrocyte sedimentation rate or of C-reactive protein levels, since giant cell arteritis can present in this way.

In rare cases, there have been (possibly coincidental) associations with malignant disorders. Being so very uncommon, this possibility does not require diagnostic testing in most cases. It does help to be aware of the risk, however, and to plan accordingly. Patients with a history of breast carcinoma, for instance, should have an imaging procedure to rule out an orbital metastasis.

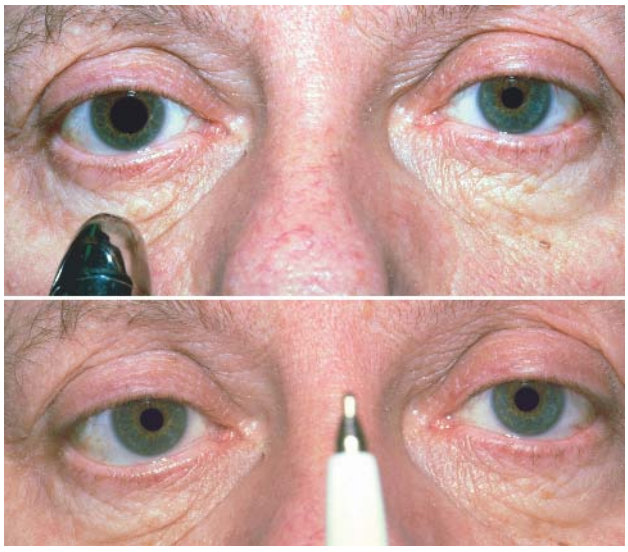


Fig. 5.5. Behavior of the pupil in pupillotonia. The light reaction is nearly gone (*above*), while the near reaction is easily detectable, though slow to respond (*below*)

see also Video 5.4

see also Video 5.5

The diagnosis can usually be made with confidence by means of simple inspection and slit-lamp examination. The pupil is frequently irregularly oval or out-of-round, appears to be unresponsive to light, and has a characteristic slit-lamp appearance in which small sectors of the pupillary sphincter can be seen to contract in a random fashion that is not related to light stimuli.

Acutely, the tonic pupil is enlarged, but shrinks gradually over a period of a year or more. It can become so small that the diagnosis is not suspected until the slit-lamp examination, where the typical segmental sphincter movements can be seen. The near response is demonstrable in all but the most acute cases (■ Fig. 5.5). This comes about when the neurons of the ciliary ganglion regenerate to reinnervate the pupillary sphincter. This is thought to be a disordered reinnervation in which the original neurons fail to reach the sphincter, and are replaced by neurons originally serving to innervate the ciliary body. The near response can be even greater in amplitude than that in the unaffected side, but the near response is always much slower, requiring a prolonged and maximal effort at accommodation. A convenient stimulus for prolonged accommodation is to use the patient's own sense of proprioception. By focusing on his or her thumb, as the digit is gradually drawn closer to the eye a slow miosis can be seen. Redilation after stopping the accommodative effort will be equally slow, hence the term tonic pupil.

Another explanation for this behavior has been suggested. Rather than faulty reinnervation, it has been proposed that the sphincter does not actually regain its innervation, but is stimulated by acetylcholine that is released from the ciliary body. It is then washed by the aqueous flow toward the pupil, causing the sphincter to contract. In addition, since it requires time for the transmitter to be washed out of the posterior chamber, the redilation phase is similarly slowed.

The tonicity is what distinguishes this sort of pupillary abnormality from the paresis caused by a lesion of the oculomotor nerve proximal to the ciliary ganglion or in the dorsal midbrain. When the near response is still partially maintained, redirection of visual attention from near to far produces a relatively brisk redilation that is quite normal. Like the tonic pupillary response to near, accommodation is also recovered in an abnormal form that is slow and incomplete. For younger patients, bifocal or progressive addition reading segments may be required prior to the usual age of presbyopia.

Tonic pupils will constrict readily in response to the instillation of a weak (0.1%) solution of pilocarpine. This response is typical, though not specific.

Pearl

If the patient feels that weak pilocarpine improves vision, this can be used as a symptomatic form of therapy. However, most patients seem to find the inconvenience of treatment and the partial relief obtained as insufficient reason to continue use of the drops infinitely. For those concerned with the appearance of unilateral mydriasis, the weak pilocarpine can be used cosmetically to temporarily mask the condition.

Tonic pupils are most commonly unilateral, but in some patients become bilateral over a variable period of several years. It is recommended that patients with a tonic pupil in one or both eyes be given documents that identify the condition, with luck sparing them unnecessary interventions when being seen in emergency rooms.

Pupillary Involvement in Oculomotor Paralysis

Oculomotor paralyses are caused by damage to the third cranial nerve at locations between the oculomotor nucleus and the ciliary ganglion. Aside from very infrequent exceptions, the extraocular muscles innervated by the nerve will to one degree or another manifest the clinical signs of paralysis, i.e., a nonconcomitant strabismus.

Pupillary mydriasis caused by internal ophthalmoplegia as part of a third nerve palsy indicates a high probability of a compressive mechanism, such as by a tumor or an aneurysm (■ Fig. 5.6). Diagnostic evaluation must be immediate and complete, up to and including cerebral angiography. An oculomotor paralysis without pupillary

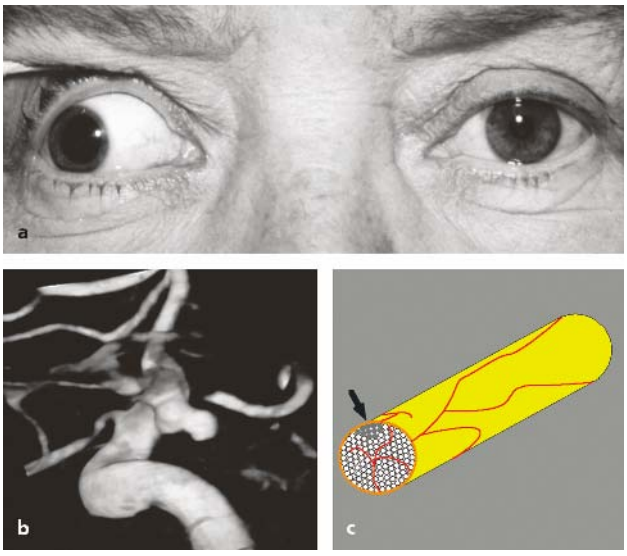


Fig. 5.6. Oculomotor nerve paralysis with pupillary involvement (**a**) is closely associated with aneurysms (**b**) and tumors. The parasympathetic fibers lie on the exterior surface of the nerve (**c**, *arrow*) exposing them to damage when the oculomotor nerve is compromised by an external mass effect

involvement suggests a less emergent condition and can be approached in a more relaxed fashion, particularly when the patient is older and has associated risk factors for small vessel disease. This association is due to the anatomy of the autonomic portion of the oculomotor nerve within the subarachnoid space. The preganglionic fibers are situated on the external surface of the nerve, where they are easily damaged by compressive lesions that put mechanical pressure on the nerve. Ischemia caused by nonperfusion of a small vessel supplying blood to the core of the nerve, as is common in patients with diabetes and/or hypertension, is more likely to spare the autonomic fibers, since the smaller autonomic fibers have lower metabolic requirements and are in closer contact with the cerebrospinal fluid, receiving their oxygen supply in part through the cerebrospinal fluid and in part from vessels lying directly on the external surface of the nerve.

see also Video 10.6

Aberrant regeneration, in which the pupil constricts in response to (most commonly) attempted adduction or depression, is a clear sign of oculomotor paresis by a mechanical mechanism, such as by trauma or by compressive lesions. The damaged axons reinnervate the extra ocular muscles in a disorganized way, causing a pathological synkinesis. The upper lid is also affected in many cases, producing a retraction of the upper lid in response to attempted adduction or depression (often called a pseudo–von Graefe sign). If aberrant regeneration develops gradually in company with a progressive loss of third nerve function, it is referred to as primary aberrancy. This is most often a sign of a slowly growing mass lesion in the cavernous sinus. An uncommon variant of this presentation includes a combined sixth and third nerve paralysis with signs of aberrant movement and simultaneous constriction of the pupil on attempted abduction.

see also Video 10.7

Lesions of the Dorsal Midbrain: Parinaud's Syndrome

Definition

Damage to the pretectal region of the dorsal midbrain producing a deficit in the light reactions of the pupil, retained accommodative miosis, and loss of connection to the Edinger-Westphal nucleus and the final common pathway of third nerve function. The clinical presentation of this syndrome includes loss of upward saccadic movements, and convergence retraction nystagmus. The entire constellation of signs is referred to as **Parinaud's syndrome** (see Chap. 11).

The cause is most commonly a pinealoma with compression of the quadrigeminal plate from above, also causing obstruction of cerebral spinal fluid flow and signs of papilledema. Lesions arising within the midbrain (usually among older patients) are usually ischemic in nature and can cause more widespread damage, with complex neurological deficits.

Pearl

Detection of the clinical signs of this syndrome mandates imaging of the midbrain and the surrounding structures.

Lesions of the Iris

Mechanically distorting lesions of the iris are easily identified at the slit lamp. One can find even subtle tears in the iris sphincter with associated loss of the of the pupil's circular shape. An attack of angle closure glaucoma typically causes a mid-dilated pupil that is unresponsive to a light stimulus. Unintended topical application of parasympatholytic agents (a so-called pharmacologic pupil) can be confirmed by instillation of 1% pilocarpine, which will have no effect on the size of the pupil. The cause is usually either contact with a pharmacologic agent or exposure to plant materials containing scopolamine (■ Fig. 5.7).

Poster 5.1

Fig. 5.7. Datura suaveolens, D. aurea and D. candida may cause dilated pupils because they contain scopolamine

Uncommon Pupillary Disturbances

Argyll-Robertson Pupils

Argyll-Robertson pupils are characterized by bilateral miosis, no responses to light stimuli, a preserved near response, and little or no response to mydriatics. They have been reported in cases in the late stages of tertiary neurosyphilis. We have seen many cases that mimic this appearance, but in which segmental pupil sphincter activity clearly labeled them as long-standing cases of tonic pupillary syndrome. Serological tests for luetic disease were negative in all instances. In those cases that suggest the diagnosis of Argyll-Robertson pupils, a fluorescent treponemal antibody absorption test (FTA-abs) test should be done, although the probability of a positive finding is low.

Intermittent Mydriasis

Definition

Intermittent mydriasis appears as an abrupt enlargement of the pupil, lasting 5 to 60 min, and it is unassociated with signs of visual loss.

The diagnosis of intermittent mydriasis (■ Table 5.3) is complicated by the absence of findings at the time of the examination, including normal pharmacologic tests of pupil function. It is very unlikely that these episodes will be linked to any credible threat to the patient's vision. When the time course is typical, it can usually be concluded that this is a form of migraine aura. It could also be an expression of sympathetic hyperactivity or a passing parasympathetic deficit. In the latter case, it could conceivably be a sign of a compressive lesion. The patient should be instructed to keep records during subsequent episodes, detailing changes in the light reaction, the interpalpebral lid fissure, and the near response, which can be done with the help of a member of the patient's family. If the initial findings suggest a parasympathetic paresis, further study should be done, using the same tests as for an oculomotor paralysis. Neuroradiologic diagnosis by MRI, including gadolinium enhancement and MRI angiography, is the preferred test. The probability of an aneurysm being the cause is very low, as long as the mydriasis is not associated with signs of oculomotor paralysis. Cerebral angiography should be considered, if there are signs of paresis of the extraocular muscles. Sometimes the eye with the smaller pupil is the problem, as in Horner's syndrome.

Table 5.3. Intermittent mydriasis: sympathetic or parasympathetic?

	Sympathetic hyperactivity	Parasympathetic paresis
Pupillary light response	Present or weak	Absent or strongly suppressed
Interpalpebral fissure	Larger than in the contralateral eye	Smaller than in the contralateral eye
Amplitude of accommodation	Normal or minimally reduced	Markedly reduced

Tadpole-Shaped Pupil

If hypersympathetic activity affects only a portion of the pupillary dilators, the pupil loses its normal, circular shape. The result is an irregular oval shape or a circle with a narrow segment that extends in the direction of the affected dilators, producing a shape that has been likened to that of a tadpole. This variant is not common, but it is occasionally described by affected patients. The basis for this behavior is unknown, but it is often encountered in patients with a prior history of migraine. If the ophthalmic examination is normal between episodes, it is not necessary to do any additional workup, as this phenomenon is thought to be benign.

Paradoxical Pupils

A paradoxical pupillary response to a light (constriction in the dark) has been associated with heredofamilial retinal dystrophies. In our experience, this condition is rare.

Congenital Miosis and Persistent Mydriasis

Two anomalies of pupillary size are of clinical importance, one is congenital miosis, and the other is a persistent mydriasis that develops during the second or third decade of age. Congenital miosis is associated with tapetoretinal degenerations but can be an isolated finding. An asymmetric mydriasis, acquired in adults, has been reported in a large group of patients in Labrador and is probably hereditary.

Normal Pupil Size?

The variance of normal pupil sizes is very large. It is practically impossible to establish limiting values for normal pupil sizes. In addition, pupil sizes change with age. Starting at puberty, the pupils have a steady rate of decrease in pupil size that averages 0.04 mm/year. This is presumed caused by a steady decrease in the centrally controlled level of sympathetic activity. In general, older people consequently have smaller pupils than do younger people.

Medications and drugs that affect autonomic neural activity can change the pupil's diameter. The normal range of pupil diameters is so large that they have little diagnostic meaning. The effects of systemic medications are always bilateral. Opiates produce a marked miosis.

Occasionally patients have bilaterally large pupils that respond poorly to light, without there being any other signs of pathology. In these cases, the tonus of sympathetic activity is markedly elevated, most commonly caused by anxiety. Later during the examination, the pupils will often revert to their usual size, as the patient becomes more comfortable with the situation.

Control of the Pupil's Size

The resting diameter of the pupil is primarily (and in the dark exclusively) controlled by the central level of sympathetic activity. Strong emotional states produce a mydriasis that can be impressive. Sympathetic regulation of the pupil size acts by stimulating the smooth muscle cells of the dilator pupillae muscle. This muscle is, however, a weak opponent of the much stronger parasympathetic sphincter muscle, which is controlled by central inhibition of parasympathetic activity. This arises from neurons in the brainstem that are noradrenergically controlled by a center in the hypothalamus. The second channel of inhibition arises in the locus ceruleus (which also controls the phases of sleep) and reaches the Edinger-Westphal nucleus in the oculomotor complex. Currently the neurotransmitter is thought to be gamma-aminobutyric acid (GABA). The sympathetic effect on the pupil thus involves a direct stimulus of the pupillary dilator muscle and a dual channel of inhibition to the iris sphincter.

Oscillations of the Pupil

The size of the pupil under all conditions of illumination has continuous oscillatory movements. These are often not visible to the naked eye. When visible, they are often said to show a state of pupillary unrest. This is a physiologic phenomenon. In the past, and still used in current publications, this has been called hippus (from the Greek word for "horse"). This is an unfortunate term, since it refers to a highly variable phenomenon that is not well defined. A better term would be spontaneous pupillary oscillations. There are two principal forms, light-induced and vigilance-dependent pupillary oscillations.

Light-Induced Pupillary Oscillations

Oscillatory variations in pupil size are thought to be a characteristic of the regulatory mechanism. At low levels of light, the light-induced oscillations are most apparent. The amplitude and frequency of these oscillations varies considerably in the same person and in comparisons between all members of any group. They can be barely visible or very striking. There are no normative values for physiologic, light-induced pupillary unrest. For this reason, it makes no sense to attempt to quantify the oscillations. True, particularly large amplitude oscillations can be seen in life-threatening circumstances, such as in Cheyne-Stokes breathing. However, such striking oscillations by themselves are never a sign of serious illness. Anxious patients are sometimes bothered by oscillations of the pupil, mistakenly assuming they are a sign of serious disease. They can be relieved with a simple explanation that the phenomenon is normal.

Vigilance-Dependent Pupillary Oscillations ("Sleepiness Waves")

When one is sleepy and in the dark, the pupil acquires a slow (<1 Hz) oscillation, with an amplitude of up to several millimeters. These oscillations can often be seen in a drowsy patient during an ophthalmic examination in a darkened room, and they are striking in their appearance. They are usually obscured by light-induced oscillations, as long as there is some light in the room. In recent years, the phenomenon of sleepiness waves has been used as an objective method for measuring daytime sleepiness. Registration of pupillary oscillations in the pupillographic sleepiness test is

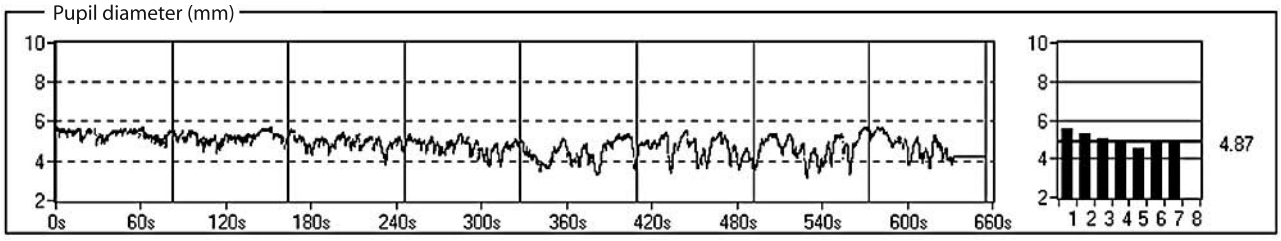


Fig. 5.8. Pupillary behavior, recorded over a 10.5-min period, in a patient with sleep apnea syndrome. In the third minute, slow oscillations of the pupil's diameter appear and then gradually increase. This is an objective sign of a strong, soporific effect. The diagram to the *right* gives the average pupillary diameter for each time unit of recording

done by infrared pupillography (■ Fig. 5.8). The sleepiness waves become more prominent in healthy people when they are sleep deprived (■ Fig. 5.8). The fatigue-related oscillations subside if the daytime sleepiness is reduced.

Sleepiness waves stem from the decreasing sympathetic tonus that accompanies fatigue, and they are a direct expression of the level of central nervous system activity. The abovementioned sympathetic inhibition of the Edinger-Westphal nucleus diminishes and becomes unstable. The pupil's diameter diminishes and wide swings of dilation and constriction appear.

Conclusion

Testing the pupil's reactions to photic and accommodative stimuli is a key part of any ophthalmic examination. They require little effort and often bring out important facts relative to the patient's vision and health. Without exception, disorders of pupillomotor function should be evaluated by an ophthalmologist as a part of the patient's evaluation and treatment. Relevant history taking to determine the source of a Horner's syndrome should be systematic and complete. It often happens that the pathogenic source of the pupillary findings is identified only after careful history taking. The ophthalmic physician can reassure the patient, and explain that the phenomenon is harmless, e.g., when physiologic anisocoria or a tonic pupil is the cause.

Further Reading

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Chapter 6

Dyschromatopsias Associated with Neuro-Ophthalmic Disease

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People with congenital dyschromatopsias are frequently not aware that their color perception differs from those with normal, trichromatic color vision. Others have learned to adapt to their limited perception of certain colors. Thus, a person with faulty red/green color discrimination will often describe a dark green color as red. Some of these people know that they cannot properly identify colors accurately in certain ranges of hue and luminance. Patients with acquired dyschromatopsias are often unaware of the changes in their color perception, due to the subtle onset and gradual progression of the damage. Not infrequently, this allows major color vision disturbances to go unnoticed. Unilateral dyschromatopsias – if not associated with cataract – should be examined with tests of color saturation in the affected eye, since this is frequently the clinical presentation for an optic neuropathy. Other neuro-ophthalmic disorders (see ■ Table 6.1) should initiate a targeted search for an acquired dyschromatopsia.

Table 6.1. Signs and symptoms indicating that one should test for a specific type of dyschromatopsia

Signs and symptoms	Suspected diagnoses	Tests (a partial selection)
Monocular loss of acuity	Desaturation, or a red/green color deficit as a sign of optic neuropathy or a tritan (blue) deficit suggesting macular disease.	Color saturation screening test with the panel D-15 or a complete Farnsworth-Munsell 100-hue test
Bilateral loss of acuity or visual field loss	Chorioretinal dystrophies, toxic retinopathy, cerebral disease	Velhagen, Hardy-Rand-Rittler plates I and II, panel D-15, Roth 28-hue, Farnsworth-Munsell 100 hue
Nystagmus	Congenital nystagmus, albinism, cone monochromacy, blue cone monochromacy	Blue/yellow plates, Roth 28-hue, Farnsworth-Munsell 100-hue
Dyschromatopsia	Congenital red/green dyschromatopsia, toxic retinopathy or optic neuropathy, (particularly pronounced in patients with antecedent congenital red/green color deficits)	Ishihara-Plates, anomaloscopy, Farnsworth-Munsell 100 hue

Fundamentals of Color Vision

Intact color perception requires a high level of performance from the human visual system. The three types of cone photoreceptors with their absorption maxima at 580, 535, and 440 nm, and their postsynaptic neurons function together in a balanced process, integrating their signals to produce an extraordinary range of color discrimination. This is why even the smallest disturbances of retinal metabolism can produce large changes in color perception. Neural processing of the information gathered by the cones begins within the retina itself. The neural net of the retina contains opponent color neurons that interact with one another to encode several channels of color and brightness perception. The spectral properties of the cone pigments and the synaptic connections between the photoreceptors and downstream elements of the retinal neural net are organized into two primary opponent channels, a red/green channel and a blue/yellow channel. This is the physiologic basis for the detection of color contrast, which is separate and apart from the processing of brightness (luminance) perception. Numerous metabolic, toxic, and inherited retinal diseases can alter the photoreceptors, their synapses, the interneurons, bipolar cells, amacrine cells, and retinal ganglion cells. Changes in transmitter metabolism can alter the balanced state of photoreceptor interactions, resulting in a disturbance of color perception. For this reason, color vision deficits are often the presenting visual abnormality for many diseases.

Colors seen by a normal trichromat (an observer with normal contributions from all three cone pigments) can be organized into a three-dimensional space (called a color model), defined by hue, saturation, and brightness. The 3D model has the appearance of an oblate spheroid with a central vertical axis defining brightness, while planes orthogonal to the axis encode hue as the various loci around the circumference of the model (with the order of hues arranged to match that of the natural spectrum), and saturation loci along the radial lines from the central axis to the external surface of the model. Locations close to the central axis have low saturation (pale, gray, or pastel), while those close to the surface are highly saturated (have the maximum "purity" of the hue in question). If we section a plane through the model in a horizontal orientation (perpendicular to the vertical axis), the plane surface thus created contains many hues, all of identical brightness, as diagramed by the color triangle in ■ Fig. 6.1. Dyschromatopsias cause pathologic changes in the size and shape of the 3D color model. The affected colors (that are confused with one another) lie along straight lines drawn through the model. These are called color confusion lines. Nearly all clinical tests of color vision are meant to determine the extent of the confusion along one or more of these lines.

In area V_1 of the visual cortex, the encoded (opponent) color channels that originate in the cell bodies of neurons in the lateral geniculate body provide the afferent flow of color information at the cortex. The various color opponents (blue/yellow and red/green) are segregated into vesicle-shaped regions of the cortex called blobs that are responsible for processing the afferent color information. The output of their processing is then sent on to higher visual centers that are responsible for higher levels of color perception (e.g., Area V_4). Occasionally, cases of faulty cortical function have been associated with unusual types of dyschromatopsias.

Color Vision Tests

Although it makes sense to use quantitative tests of color vision (e.g., with the Farnsworth-Munsell 100-hue test) when following patients being treated with chloroquine or similar drugs, this is a time consuming, tedious and therefore expensive test that requires the close attention of a trained assistant for periods of up to an hour. Simpler and quicker tests are available to be used when there is a suspicion of an optic neuropathy. Tests of color saturation perception (e.g., color discrimination along one line of color confusion at constant hue and brightness) are strongly correlated with optic nerve disease. Quick tests are needed, given the high incidence of optic neuropathies.

The number of available color vision tests exceeds the necessary repertoire by far. It makes sense to choose a small group from among the tests that are explained in the following section, building one's own little "tool box."

Testing the Discrimination of Color Saturation

Light seen by an eye with an optic neuropathy appears darker than when seen with the contralateral (normal) eye. Colors fade, lose their vibrancy, and appear darkened. This can be detected simply by using the red cap from a bottle of a mydriatic preparation. With both eyes open, the bottle cap is shown to one eye or the other by alternating monocular occlusion. Patients with macular disease in the early stages do not see any change in the saturation (richness) of the red color. At the onset of a serous elevation of the macula (usually monocular at first), the patient will note a striking difference in the appearance through one eye as compared with the other. Using a red test object, one can simultaneously screen for defects in luminance perception at the long-wavelength (red) end of the color spectrum.

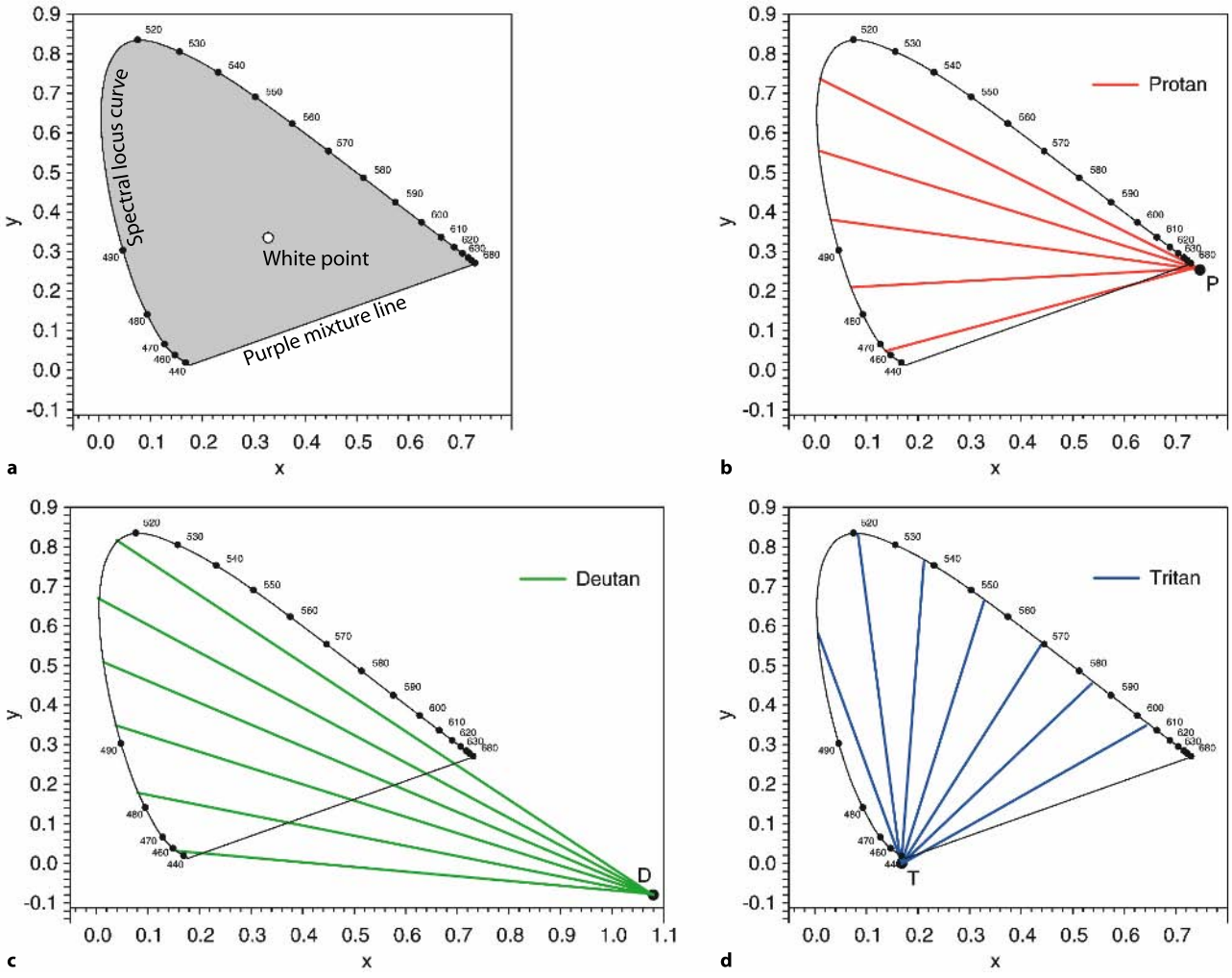


Fig. 6.1. The International Commission on Illumination (Commission Internationale de l'Eclairage – CIE) chromaticity diagram (**a**) is bordered by the locus of spectral colors (*curved line*) and the violet (*straight*) line that connects the two ends of the spectral locus curve. The diagram represents a plane section through the color space (of the human eye), orthogonal to the axis of luminance, meaning that all colors represented in this section of color space are of equal brightness. The triangular shape arises from the three cone types of varying spectral sensitivity that define the limits of color space in all three directions. If all three cone types are stimulated to a proportionally balanced extent, the resulting sensation is a colorless white (marked by the region with the white point). If one of the cone types is missing, the colors that depend on that cone type for distinction from other colors will appear identical, called color confusion. In protan and deutan color deficits, colors that vary in their content of red versus green appear more alike, while in tritan deficits, colors that differ by their relative content of blue versus yellow become indistinguishable. Such colors lie along the protan (**b**) deutan (**c**), or tritan (**d**) lines of confusion. Pseudoisochromatic plates use colors taken from a series of points along one of the confusion lines. In acquired dyschromatopsias caused by neuro-ophthalmic diseases, signal interactions between the inputs of the three cones types are weakened. This causes an increasingly large, colorless area surrounding and expanding from the white point in the direction of the affected interaction

Note

Hue discrimination and brightness comparisons are subjective tests. Careful observers with normal vision will occasionally notice spontaneous variations in color when comparing one eye with the other, yet responses are not always precise, and there are frequent false-positive responses. Variations in light adaptation when comparing one eye with the other – which can be the case immediately after monocular opthalmoscopy – will cause transient periods of interocular color and brightness disparities.

Pseudoisochromatic Plates

Definition

Isochromatic means very similar or identical color appearances. **Pseudoisochromatic** means that observers with color deficiencies will see foreground and background of figures as indistinguishable (equally colored and equally bright), and will be unable to see the patterns, while those with normal trichromatic vision will see the embedded characters.

The principle of the color plates can be diagrammed by placing the various shades of color in the International Commission on Illumination (Commission Internationale de l'Eclairage – CIE) color triangle (see ■ Fig. 6.1). The lines are loci of isochromatic stimuli for those with color deficiencies, and the various spots or elements of the image are chosen to fall along these lines. While the color contrast is evident to the normal trichromat, the color-deficient observer will not be able to see the figures as distinct from their background. The embedding of figures in a chaotic mixture of brighter or darker, and smaller or larger elements means that the only way to differentiate correctly a figure from its background is by color differences (■ Fig. 6.2).

Since disorders of color perception can also change brightness sensitivity, separate groups of plates must be used for the detection of congenital versus acquired dyschromatopsias.

A group of pseudoisochromatic plates has been developed for recognition of the most common forms of congenital color vision deficiencies (e.g., Ishihara plates for the detection of congenital red/green color deficiencies). There are also plates specifically designed for the detection of acquired dyschromatopsias (e.g., the Velhagen-Broschmann plates, or the SPP 2-plates according to Ishikawa), which in part have pseudoisochromatic stimuli for detecting deficiencies of blue perception. Both types of plates should be available for use.

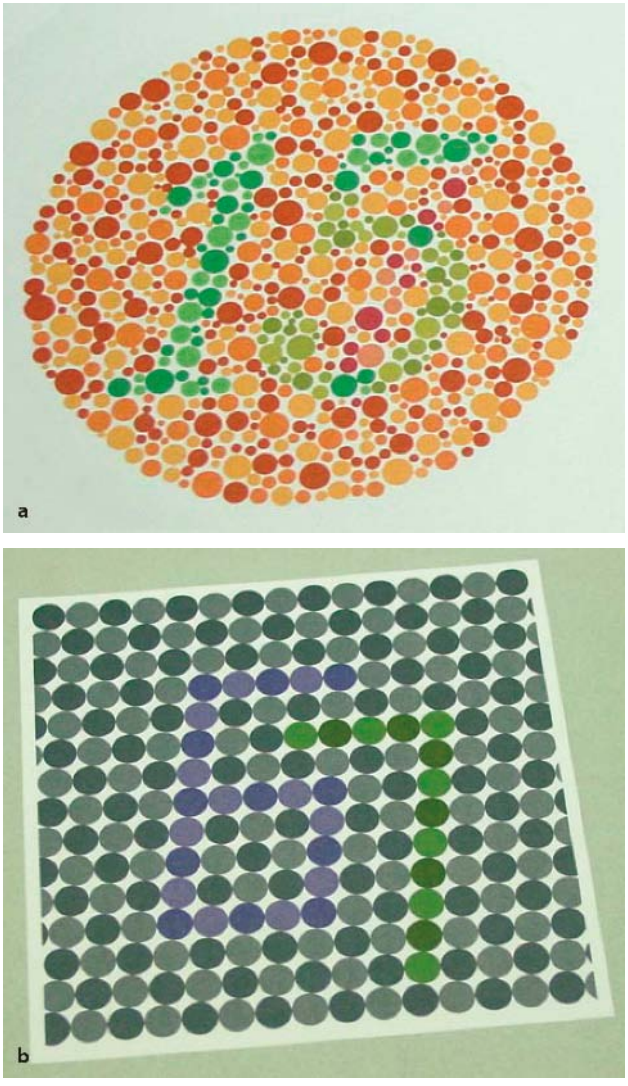


Fig. 6.2. a Pseudoisochromatic plates for the detection of red/green dyschromatopsias (Ishihara). The colors of the optotypes and their backgrounds are taken from one of the respective lines of color confusion. Normal trichromats will be able to see the contrast between optotypes and surround, but those with the respective dyschromatopsia will not. (The figures shown here are for instructional purposes only and are not suited to the testing of color vision.) **b** Pseudoisochromatic plates for the detection of a tritanopic reduction in blue perception (Velhagen, Broschmann). The colors are all taken from a tritan confusion line, and will be difficult to distinguish by an eye that has poor blue/yellow discrimination

Color Sorting Tests

The subject being tested is asked to sort colored elements in a continuous sequence of hues that together form a circle in the color triangle, surrounding the white point at the center (■ Fig. 6.3). For suspected congenital and for most of the pronounced color vision deficiencies, the saturated color tests may be used, while for acquired and for subtle disorders, mostly desaturated (pale) colors are used. For initial testing one can use the Farnsworth panel D-15 test (in the saturated or the desaturated form, according to Lanthony) or the more quantitative Roth 28-hue test (also available in both saturated and desaturated forms). For a more precise, quantitative determination, the Farnsworth-Munsell 100-hue test with 85 colored caps can be used.

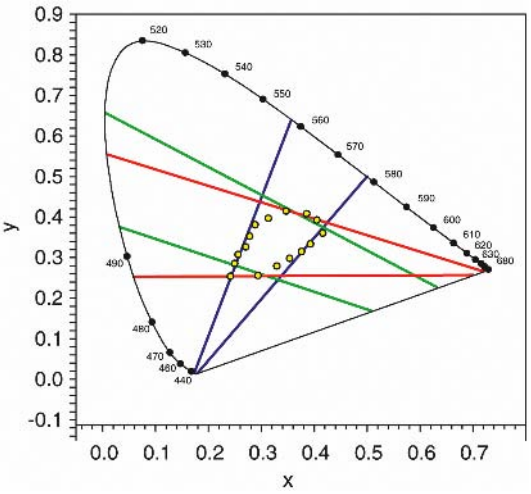


Fig. 6.3. The CIE chromaticity diagram with the locations of the colored test caps used in the panel D-15 color ordering test. These colors fall on an oval contour that surrounds the neutral white point. The distances between cap colors and the white point are proportional to the color saturation of the cap colors. The lines of color confusion cross the test's color circle at varying angles. Patients with normal color perception will order the caps correctly, while those with dyschromatopsias will show sorting errors that fall parallel to lines that are approximately tangential to the color circle

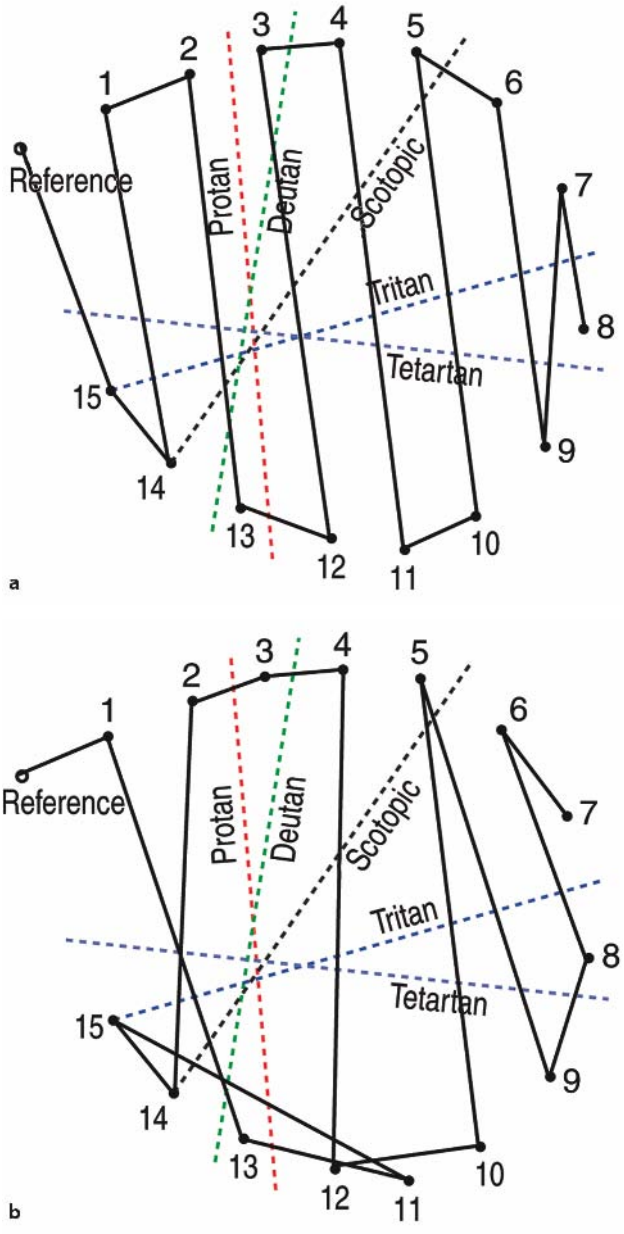


Fig. 6.4. **a** The color confusion lines of congenital color defects (e.g., for a protanopia) have an orderly pattern and are very nearly parallel to one another. **b** In acquired disturbances of color vision (e.g., Stargardt's disease) errors of color confusion can develop at many different angles

Note

Since subjects with altered brightness sensitivity can sometimes rely on achromatic brightness differences (varying levels of gray) to sort a color sequence, they can sometimes produce a correct sequence in spite of having a significant color vision deficiency. For this reason, it is especially important to use a standardized illumination (e.g., the Macbeth table lamp or light boxes with normative light "C" [6,775 K] or "D65" [6,500 K]) for all color testing with reflective sorting elements. The luminance level should be 500 to 1,000 lux.

For each cone type there is a group of lines of color confusion that converge on one another at a single point (■ Fig. 6.4). The position of this point is different for each of the cone types. Patients fail to differentiate those colors that fall along one of the color confusion lines in the color triangle. Given the orientation of the axis of confusion determined by this test, one can deduce the nature of the patient's color vision disorder. Transpositional errors that lie parallel to the color confusion lines for a protan defect indicate a disturbance of the long-wavelength red cone mechanism, an orientation of transpositional errors parallel to the deutan group of color confusion lines is consistent with a disorder of the medium-wavelength green cone mechanism, and sorting errors that fall on lines parallel to the tritan family of lines suggests a disturbance of the short-wavelength blue cone mechanism. The severity of the disorder can be quantified by the number and size of the transpositional errors, calculated as a sum of the errors.

Pearl

For congenital color deficiencies the errors tend to be aligned in highly ordered groups, with a high reproducibility and converging on a single point in the color triangle. Acquired dyschromatopsias more commonly produce transpositional errors aligned toward two or even all three of the corners (see ■ Fig. 6.4). Additionally, the level of illumination has an influence. While cone dystrophies tend to yield increasing transpositional errors as luminance levels are increased, deficits associated with maculopathies and optic neuropathies tend to worsen as the luminance levels are decreased.

Note

Many patients will show a significant learning effect during the administration of these tests. It is best to verify abnormal results rather than accept the results of a single test. Errors that are parallel to the tritan axis (which is roughly tangential to the upper and lower segments of the color/circle in the panel D-15 test, i.e., color caps 2–6 and 9–14) are particularly prone to be the result of careless mistakes and can closely mimic the appearance of a blue deficit in color vision.

Anomaloscopy

An exact classification of a red/green color dyschromatopsia can be determined with a spectral instrument called the anomaloscope. The subject to be tested is shown a semicircle with a mixture of red and green spectral lights that he/she can change, and he/she is then asked to adjust the brightness of the mixture to match that of a yellow semicircle (the two semicircles abut one another to form a full circle) so that the two halves of the circle appear to be most nearly alike in color and brightness. (This is the so-called Rayleigh equation; see ■ Fig. 6.5.) Normal subjects can produce a match with only a narrow range of mixtures, while subjects with red/green dyschromatopsias can produce matches of the same kind over a much larger range of red/green mixtures.

The evaluation form (according to Pitt, ■ Fig. 6.6) and the procedural and testing data forms (■ Fig. 6.7) are designed to assist with proper completion of the test, recording of the results, and calculation of the anomaly quotient (AQ). As a rule, normal trichromats can find a match by adjusting a mixture of red and green lights in one half of the circle to match the brightness of a spectral yellow light in the other half circle, such that the two halves appear equal in hue and intensity. (A normal subject's equation typically averages 40 scale units and must lie between values of 36.5 and 43.8 scale units to be considered normal. This corresponds to an AQ of 0.7 to 1.4.) A subject with a congenital, X-linked red and/or green sensory deficit, depending on the type, will show a higher red or green component needed to produce a match, than will a normal subject. The values chosen by the test subject with a protanomaly will be found to parallel the protan axis when recorded in the Pitt diagram, while the values chosen by a subject with a deuteranomaly will be arrayed along lines parallel to the deutan axis (■ Fig. 6.6). Dichromats – i.e., protanopes and deuteranopes – when adjusting the red and green components find acceptable matches (meaning of equal brightness and color) to the spectral yellow light with varying mixtures of red and green across the entire scale of values from 0 to 73 (■ Fig. 6.6). The differentiation of protanopia from deuteranopia is made based on the differences in the brightness distribution of the matches for the two types of dyschromatopsia. In subjects with achromatopsia, where there is a loss of both the red and green cone inputs, brightness perception is determined by the rods. Red light appears very dark, which can be inferred from the marked

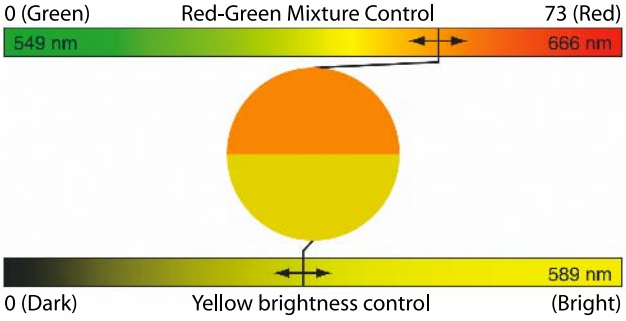


Fig. 6.5. Rayleigh spectral matching in anomaloscopy. The subject is asked to fix attention on a circular test field that must subtend a visual angle of 2°. The upper half contains the additive mixture of green and red spectral lights, 549 and 666 nm, while the lower half is the comparison yellow light at 589 nm. The red and green components of the mixture in the upper half are continuously variable in small steps (0 to 73 or 0 to 100), with the scale value of 0 indicating a completely red-free stimulus, and the scale value of 73 (or 100) is a stimulus devoid of green spectral light. The scaling of 0 to 73 was used in the original anomaloscope developed by Nagel. The value for the proportioned mixture that matches the appearance of the spectral yellow light for eyes with normal trichromacy is 40 (36.5 to 43.8), when using a scaling of 0 to 73, but will have a scale value of 50 for those instruments that use a scaling of 0 to 100. The brightness of the comparison yellow light is continuously variable; the norm for most testing is a setting of 15 units ±2. Color-neutral adaptation with a gray/white light is maintained throughout the testing by using the neutral field about 50% of the time, switching from color to neutral and back to color again at 3-s intervals. Anomaloscopes for determining the Rayleigh equation must match the wavelengths bandwidth, visual angle of the testfield, and must have a luminance value according to DIN 6160

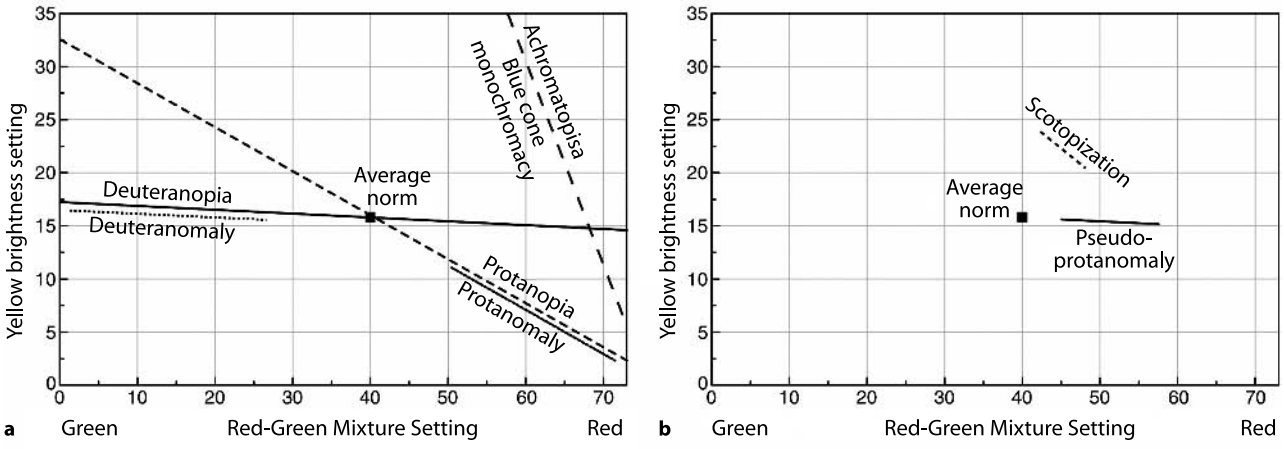


Fig. 6.6. Diagram according to Pitt for recording and plotting the examination results for the Rayleigh equation. The ordinate shows the brightness of the yellow comparison light, with the abscissa showing the brightness of the red/green mixture. The results for the Rayleigh equation are expressed in scale units or as the anomaly quotient, AQ. The conversion is made by using the formula:

$$AQ = \frac{M_n * (73 - M_p)}{(73 - M_n) * M_p},$$

where M_n stands for the scale reading of the red/green mixture control for a normal trichromat and M_p for the value set by the patient. Some instruments will do the conversion automatically. A reading of 40 (average normal) corresponds to an AQ of 1.0, a reading of 73 to an AQ of 0, and a reading of 10 to an AQ of 7.6. For instruments with scale divisions of 0 to 100, 73 must be replaced by the value 100 in the above formula. A normal trichromat will have an AQ between 0.7 and 1.4. In cases of dichromacy, AQ is undefined, since dichromats will accept all matches (AQ = 0 – ∞). The examples of results correspond to congenital (**a**) and acquired (**b**) dyschromatopsias. For acquired disturbances, the calculation of AQ is omitted, since an acquired dyschromatopsia is not an anomaly of cone photopigments and the value for AQ has no useful meaning

reduction of brightness of the corresponding yellow field. Green light, on the contrary, appears to the rod-dependent viewer as very bright, and the brightness of the match to the yellow field is correspondingly high. Acceptable matches are found along the achromatic axis, corresponding to the long-wavelength end of the rhodopsin spectral absorption curve. In the presence of anomalous trichromacy (i.e., protanomaly or deuteranomaly), the matches chosen by a subject with normal trichromacy (e.g., a red/green mixture of 40 matched to the brightness of the spectral yellow set at 17) will be rejected by those with anomalous trichromacy; the mixed field will appear different, since the red- or green-sensitive cones produce a reduced signal, and the color sensitivity is dominated by the remaining, intact cones. So, the color matches of the deuteranomalous subject will be depressed in the green region of the diagram (e.g., at the mixture knob (MK) in a region of 10 to 20, corresponding to an AQ [see ■ Fig. 6.6] of 7.6 to 3.2), while the matches of a protanomal will tend to be in the red portions of the diagram (between 55 and 65, corresponding to an AQ of 0.39–0.15) with a correspondingly reduced brightness sensitivity. The lower brightness seen at the long-wavelength end of the spectrum is caused by a deficiency of the long wavelength (red) cones.

Use of the Anomaloscope when Determining Red/Green Matches (Rayleigh)

Correct use of the anomaloscope, as described in the procedure and documentation page (■ Fig. 6.7) and the process diagram (■ Fig. 6.8) involves several steps. During the procedure the examiner must use an intermittent (about every 3 s for 3 s at a time), neutral white light stimulus to prevent adaptation of the retinal photoreceptors to the colored test lights.

A. The examiner initially sets the controls of the instrument to a mid-normal red/green mixture (the mixture control at 40 and the spectral yellow at a brightness of 15) and asks the subject whether both halves of the field are equally bright and identically colored. If the patient accepts this match, the patient has normal color vision, deuteranopia, protanopia, or a rare form of extreme anomaly. If the patient rejects the normal match, he/she either has anomalous color vision or a normal variant of trichromacy (step A in ■ Fig. 6.7).
B. If the normal mixture is not accepted as a match, the examiner can determine in the next step whether one or both of the typical, anomalous matches are accepted (step B). The increased contrast seen particularly by deuteranomals can have the effect of not allowing any

Color Vision Tests

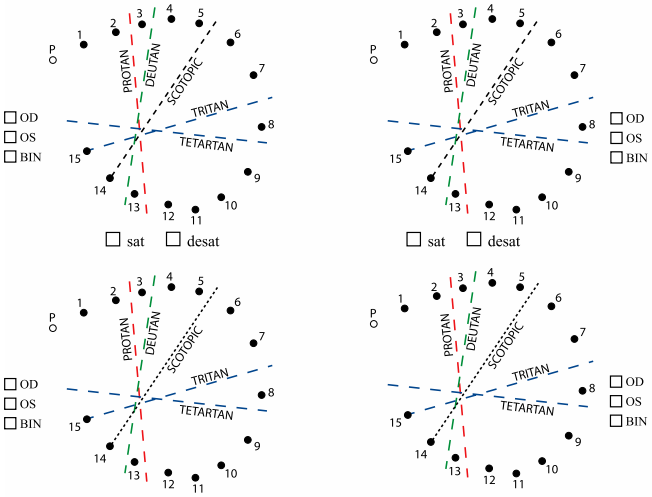
Patient [ID Stamp]

Examiner .....
Date .....
Diagnosis .....
Initial test ☐ Follow up test ☐

1 Ishihara Color Plates [at 75 cm, 3s per plate, circle missed plates]

OD ☐ OS ☐ BIN ☐	1	2	3	4	5	6	7	8	9	10	11	12
	13	14	15	16	17	18	19	20	21	22	23	24
OD ☐ OS ☐ BIN ☐	1	2	3	4	5	6	7	8	9	10	11	12
	13	14	15	16	17	18	19	20	21	22	23	24

2 Sorting Tests Panel D-15 [sat], Lanthony Panel D-15 [desat]



Adapted from: E. Zrenner, Farbsinnprüfungen (Eds. O.-E. Lund, Th. Waubke) Enke, Stuttgart, 1985

3 Anomaloscopy

Date .....
Examiner .....
OD ☐ OS ☐

A Assessment of normal matches

Mixture Knob (MK)	Yellow Knob (YK)	
40	16	Normal balance
		Subject's setting
Question: Are both hemifields identical with respect to color and brightness?		
If yes, proceed to step C.		
If no, in what colors do the hemifields appear?		

B Assessment of anomalous matches

20 (Deutan)	16	Identical? yes/ no If no, color of hemifield
60 (Protan)	8	Identical? yes/ no If no, color of hemifield

C Assessment of extreme matches

MK	Subject attempts to find at match by setting YK	Identical? (yes/ no)	If no: Color of the superior hemifield
0			
73			
		Subject attempts to find a match by setting knobs	

D Additional steps to determine the range of matches

Setting (MK)		Subject attempts to find a match by setting YK	Identical ? Unstable color apperance (within 15s)	If no: Color of the superior hemifield
Preset values	40			
	30			
	50			
	20			
	60			
	10			
	73			
	0			
Breadth of matches				

Fig. 6.7. These formes serve as standard documents for recording the results of color vision testing. During tests with the anomaloscope, scale values for the mixture control (0 to 73) and the patient's answer to the question, "Can the yellow field be made to match the mixture field in both brightness and color?" are recorded. If the answer to the question is yes, the scale value is recorded. The breadth of matches is determined in up to two trials, using the color mixture scale, recording the limiting values for the matches

match, but rather yielding an endpoint that approaches but does not fully reach a match).

C. If the normal mixture is accepted as a match, the examiner can immediately test both extremes of the red/green mixture control, to determine whether a complete protanopia or deuteranopia is present. Steps B and C also allow a quick orientation.

D. Most observers accept not just a single red/green mixture as a match to the yellow light, but rather a spread of neighboring mixtures. Starting with a setting that the subject has initially chosen as a match, the region of acceptable matches is explored. This is done in both the direction of increasingly red, and then in the direction of increasingly green mixtures. The subject is asked to find acceptable brightness matches, and then to determine color matches. The conventional measure, which is also used for certification of the test results, is the range of settings that are acceptable matches. Longer periods of testing, especially for patients with acquired color vision disorders caused by retinopathies and/or optic neuropathies, can cause an expansion of the range of matches. The repeat use of a neutral adapting field is meant to minimize this iatrogenic effect. The range of settings is recorded along with the corresponding brightness of the yellow field. For this purpose, the blank lines of the recording form are used.

If no match can be found during steps A–C, one can use test D. Initially, coarse steps of tenfold units are used for orientation, after which acceptable matches are sought in smaller, twofold steps. The range of matches for which the two halves of the test field are seen as equally bright and identically colored is then recorded. If by these smaller changes in the mixture one still cannot find a match, one

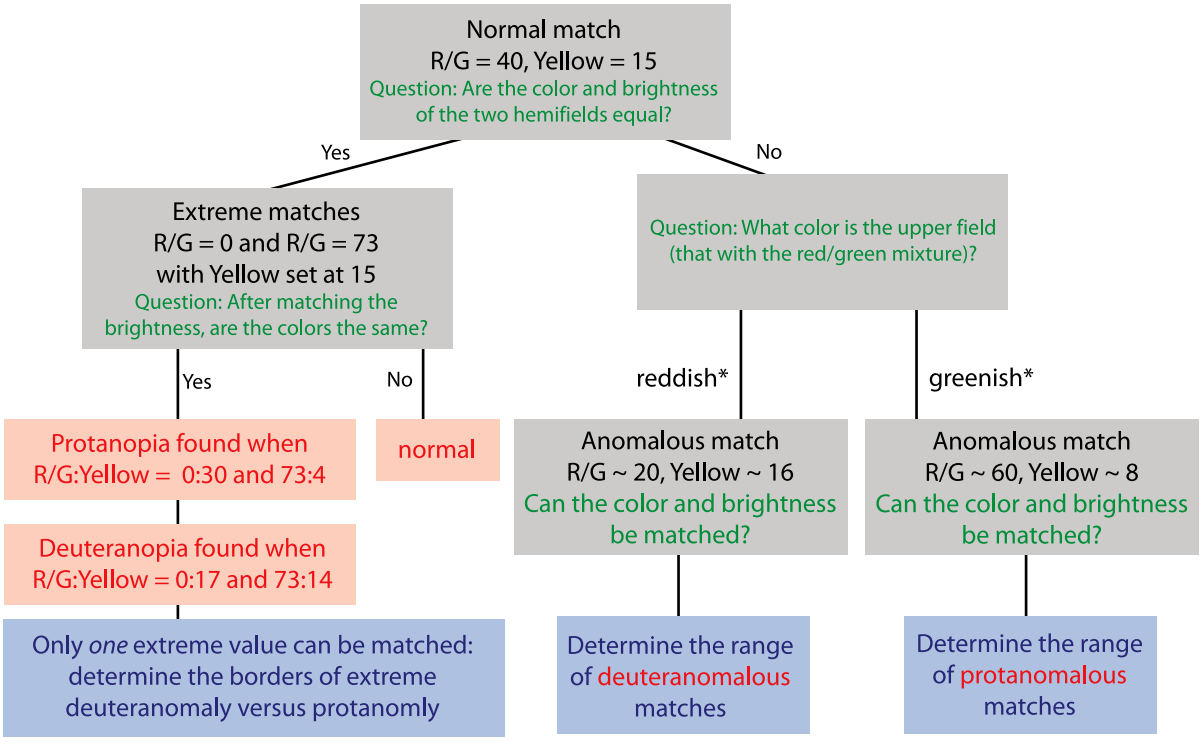


Fig. 6.8. Diagram of a specifically focused examination for a subject with a congenital red/green dyschromatopsia, using the anomaloscope. Since achromatopsia and blue cone monochromacy, given their additional symptoms, have already been ruled out, their signs are not included in this diagram. Initially, a normal match (equation) is shown and, when necessary, it is adjusted to match the brightness of the spectral yellow field. If the patient reports that there remains only a slight color difference, he/she may be asked to use the mixture control to make a small adjustment. This is necessary, since small differences of color vision are common among normal observers. While the examination of anopias (dichromats completely lacking one of the three types of cones) leads to a rapid diagnosis, Patients with anomalous trichromacy (having a reduction in but not complete absence of one of the three classes of cones), will match in the region of the corresponding anomaly. If a match can be found, a range of settings over which the match can be maintained is determined (see text). In rare instances, no acceptable matches can be found, even when using extreme settings of the mixture control. In such cases, the boundaries must be determined. The brightness curve will indicate the type of dyschromatopsia (protanomaly or deuteranomaly). * If the range of a patient's matches includes the average normal mixture, the color responses of the patient have not been conclusive; in this instance the test can be repeated while using coarse (tenfold greater) steps in the red/green mixture control to find a match that is accepted by the patient (section D in the data form of Fig. 6.7)

can record the endpoint that lies closest to a match, and then note whether the mixture is seen as "too red" or "too green," as a mark of the increased contrast found in subjects with red/green anomalies (protanomaly or deuteranomaly). Otherwise, there is an increase in suspicion of false responses.

Pearl

For calculation of the AQ, one uses the formula given in ■ Fig. 6.6, in which the accepted mixture that lies farthest from the normative value is used. Additionally, the breadth of acceptable matches is recorded in scale units, since these values increase with increasing severity of the findings. A number of anomaloscopes have an optional setting for the detection of changes in blue sensitivity.

Strategy for Testing Color Perception

The strategy used for examination of color perception is simple whenever there is suspicion of a dyschromatopsia ■ Table 6.2. While strong suspicion of an optic neuropathy makes examination of color saturation sensitivity a logical first step, for all other color disorders use of the pseudoisochromatic plates is the preferred method.

If testing with the plates finds evidence of a probable abnormality, or there is at least a clinical suspicion of a color disturbance, additional testing can help to answer the following questions: is the dyschromatopsia

- Congenital (e.g., anomalous trichromacy or achromatopsia)?
- Associated with other symptoms of a hereditary disorder (e.g., retinitis pigmentosa or dominant optic atrophy)?

Table 6.2. Congenital dyschromatopsias: frequency and mode of inheritance - dichromats and anomalous trichromats

Protanopia	1%	X-linked recessive
Protanomaly	1%	X-linked recessive
Deuteranopia	2%	X-linked recessive
Deuteranomaly	4%	X-linked recessive
Tritanopia	0.05%	Autosomal-dominant
Achromatopsia	0.003%	Various types
Blue cone monochromacy	Very rare	

- More likely to be acquired (e.g., known or suspected toxic damage, metabolic disorders, inflammatory disease or cerebral infarctions, etc.)?

For quantification and classification of a specific type of disorder, the color sorting tests should next be used as the second phase, and finally, when indicated, the anomaloscope can be used, such as for certification of the extent of the subject's color vision deficiency. This is of particular importance for occupational requirements, such as the documentation of normal vision for persons who will be operating automobiles or other heavy equipment.

Dyschromatopsias

Hereditary Disorders of Color Perception

Congenital X-linked dyschromatopsias are common (■ Table 6.3). About 8% of men and 0.4% of women are affected. In the dichromacies, a cone mechanism is faulty, while in the anomalous trichromacies, the problem is merely an alteration in the spectral curves for one or more of the cone types. When the separation between the spectral sensitivity curves of the functioning cone types is less than normal, their distinction from one another will be more difficult.

The brightness sensitivity of a protanope (red cone defect) falls sharply at the long-wavelength end of the color spectrum, while the deuteranope (green cone defect) has almost no change in brightness sensitivity

The tritanope (blue cone defect) has an abnormal spectral sensitivity at the short-wavelength end of the spectrum. Achromats or monochromats, who have only rods or only one type of cone mechanism (rare), cannot differentiate colors at all. Occasionally both red and green cones are absent, leaving the retina with rods and blue cones only, an X-linked disorder that is called blue cone monochromacy.

Pearl

Those with the rather common congenital dyschromatopsias, classified as dichromacy or anomalous trichromacy, are able to correctly differentiate hues and shades within some parts of the hue circle. They are not colorblind, but rather have a diminished capacity to discriminate among some hues that are adjacent to one another in some part of the normal gamut of color perception.

Acquired Dyschromatopsias

Acquired dyschromatopsias can be caused by degenerative diseases, toxic exposures, metabolic disorders, inflammatory diseases, and/or cerebral insults. For this reason the history taken from the patient, from other physicians participating in the patient's care, and/or from relatives of the patient, is of particular importance (■ Table 6.4). Monocu-

Table 6.3. Strategies for history taking when evaluating dyschromatopsias

History	Etiologies to consider	Suspected diagnoses and diagnostic strategies
Family history		
Mode of inheritance	Genetic defects	Examine all affected family members and possible carriers of recessive traits
Past medical history and current problems		
General symptoms fainting, headache, paresthesias, myasthenia, malabsorption	Mass lesions, demyelinating diseases, intoxication	Neurological consultation, electrophysiology, toxicology
(Prior) illnesses: liver, kidney, gastrointestinal, diabetes mellitus	Faulty excretion or metabolism of toxins, jaundice, intoxications	Internal medicine consultation
Chronic inflammatory diseases	Pigment epitheliopathies	Electrophysiology, serology
Hearing loss	Vascular, hereditary, toxic	Consider ear, nose, and throat consultation
Rheumatoid disorders, malaria, tuberculosis, migraine, psychic disorders	Drug overdose	Monitoring of duration of drug use, cumulative dose

Table 6.4. Tobacco, alcohol and other commercial products associated with losses of color discrimination

Pipe tobacco	> 30g/week, reduced chelation of trace cyanide
Methyl alcohol	Manufacture of porcelains, adhesives, rubbers, dyes, and formaldehyde
Ethyl alcohol	More than 11 glasses of wine or 3 bottles of beer per day, B12 deficiency
Lead	Manufacturing of dyes, soldering, assembly of stained-glass windows
Thallium	Rat poisons, depilatories: alopecia
Sulfur-carbon compounds	Vulcanization
Chloramphenicol	Children (!) B6 deficiency

lar dyschromatopias associated with pain on eye movement, fainting, headache, paresthesias, or muscular weakness, call immediate attention to a probable inflammatory process in or near the optic nerve. When other findings increase the level of suspicion, neurological or electrophysiological studies should be considered. Malabsorption syndromes, when combined with dyschromatopsia, can indicate a metabolic disorders or poor nutrition (such as a vitamin B_{12} deficiency). This indicates the need for appropriate serologic, endocrinologic, and/or toxicologic tests. If there is a disorder of renal or hepatic function, it is possible for the blood level of some drugs to rise, causing toxic damage to vision (e.g., chloroquine phosphate, or ethambutol). If the patient has poor hearing, this may indicate the presence of a hereditary syndrome. Questioning about the duration of prior treatment should help to discover any chronic drug overdosing. It is very important to accurately detail the duration of the medication's use and the total daily dose, such as when dealing with tuberculostatic agents, analgesics, antibiotics, psychotropic drugs, as well as agents used in managing cardiac, circulatory, and sleep disorders. It is best, depending on the specifics of the disorder, to consult standard toxicologic references, such as those of Grant, or Fraunfelder.

In addition, a history of occupational exposures to heavy metals, fumes, or chemicals should be specifically ruled out, since such disorders are frequently accompanied by color vision disturbances, especially in the early stages of the exposure (see Chap 17). Not to be missed are questions regarding the use (and misuse) of tobacco and alcohol, which can severely amplify the problems caused by B_{12} deficiencies. This in turn can lead to a severe optic neuropathy with typical central scotomas and red/green dyschromatopsias. In this setting, the blood levels of vitamin B_{12} and folic acid should be tested and the possible malabsorption of vitamin B_{12} should be ruled out, since patients with pernicious anemia frequently present with visual loss. In addition, strong environmental exposure to high levels of light can lead to dyschromatopsias, such as an acquired tritanopia caused by damage to the blue cone mechanism.

Note should be taken of the onset, duration, and course of the disorder, including questions of bilateral onset, simultaneous color disturbances, and additional symptoms like photophobia, poor dark adaptation, or coloring of images. These can indicate the presence of a toxic or heredofamilial retinal disorder with corresponding consequences.

Signs and symptoms of disorders more properly handled by internists are nonetheless important when searching for the cause of a color vision disturbance. Unusual skin color can be a sign of pernicious anemia; striking hair color and disturbances of ocular pigmentation can help one recognize oculocutaneous albinism with nystagmus. Nystagmus is not infrequently found associated with dyschromatopsias, as in rod monochromacy, or in "syndrome" albinism like Åland Island eye disease. If there is no nystagmus present, one should still inquire whether rapid eye movements were noted in the early years of childhood, since the nystagmus associated with blue cone monochromacy can completely disappear in adulthood.

Drug-Induced Dyschromatopsias

Hundreds of drugs used for the treatment of virtually every class of disease can cause an acute dyschromatopsia when administered in therapeutic doses. Most of these drug effects are minor, reversible, and are frequently overlooked. Frequently, problems arise when patients with antecedent color vision abnormalities (anomalous trichromacy or dichromacy) have their color perception further degraded by drug effects. For them, the added loss to an already-restricted color space can be profound. These patients report major problems with dyschromatopsias up to and including complete achromatopsia.

All acquired dyschromatopias are typically encountered in three different classes. Type I dyschromatopsias are red/green defects in which a so-called scotopization is present. This means that the brightness sensitivity when plotted in the Pitt diagram (■ Fig. 6.6) falls in the direction of the achromatic axis. This is not the case in type II of the acquired dyschromatopsias. Although they are also red/green disorders, the color matches in the anomaloscope lie as a rule along the deuteranopic axis. This suggests that the damage to color vision in the type I disorder is weighted toward the function of long-wavelength (red sensitive)

cones and type II toward the function of medium-wavelength (green) cones. Type III dyschromatopsias are characterized by blue/yellow hue discrimination defects. The various drugs that affect color perception are usually associated with one of these three pictures. In addition, there is a group of drugs that has oculotoxic effects when used over long periods (see Chap. 17).

As shown in ■ Table 6.5, there is a long list of substances found in tobacco and alcohol products, and some compounds released by industrial processes that have been associated with acquired dyschromatopsias.

Cerebral Dyschromatopsias

Cerebral dyschromatopsias, usually the result of stroke, arise abruptly and are often accompanied by bilateral homonymous hemianopic visual field defects in the upper quadrants, or in some cases with a prosopagnosia (see Chap. 13). The brightness distribution during color testing is normal, and anomaloscopy settings are similar to those of congenital deuteranopia.

Chromatopsias

Chromatopsias are perceptions of colors that dominate vision, causing strong casts of color, as if peering through colored glasses. Erythropsia, a pronounced shift of color perception toward the long-wavelength end of the spectrum, is often caused by exposure to very high levels of short-wavelength (blue) light. This most commonly happens in pseudophakic patients whose eyes no longer have the yellow filter provided by the native lens of the ageing eye. (Particularly on the day after a snowfall, pseudophakic patients who have been outdoors on a cloudless day will experience a striking red shift in their vision, usually after returning to indoor locations). The strong blue light in the reflected solar spectrum creates a greater bleaching of cone pigments in the shorter wavelength end of the absorption spectra, including both short and middle wavelength light. Digitalis toxicity has long been known to cause xanthopsia – a distinct yellow cast – associated with a more selective loss of blue perception, while maintaining sensitivity to both middle and long wavelengths of light. Chloropsia is much less common, but is produced by loss of visual sensitivity at the long and short-wavelength ends of the visible spectrum, while leaving the medium-wavelength sensitive (green) cones to work in relative isolation.

Patterns of Color Vision Loss in Acquired Retinopathies and Optic Neuropathies

In 1912, Köllner, an ophthalmologist in Berlin, published a monograph in which he reviewed an extensive body of literature on the nature of color vision impairment in patients with acquired disease. Principal among his observations were that most patients with diseases of the retina (especially the macula) tended to have disordered color vision characterized by a preferential loss of the ability to discriminate blue from yellow hues, while most patients with diseases of the optic nerve tended to have a greater loss of discrimination between red and green hues. This general (though by no means consistent) dichotomy of blue/yellow defects in retinal disease and red/green defects in optic nerve disease has since come to be known as Köllner's rule.

Not all cases of acquired dyschromatopsia conform neatly to Köllner's rule. Although the rule holds fairly well, significant exceptions are familiar. These consist of: (1) cases of acquired dyschromatopsias in which no clear difference can be found between the relative impairments of blue/yellow versus red/green, (2) cases in which optic nerve diseases are associated with blue/yellow discrimination defects, and (3) cases in which macular diseases are associated with predominantly red/green discrimination defects. Some diseases show a predominant blue/yellow discrimination defect in their early stages, but characteristically have mostly a red/green defect in their advanced stages. Cases have been observed in which a disease has caused an acquired, preferential loss of blue/yellow discrimination, only to change to a greater loss of red/green discrimination before finally deteriorating into a global loss of color perception.

As originally reported by Köllner, and confirmed by others, diseases of the optic nerve tend to produce acquired red/green color vision defects. Optic atrophy will frequently result in an acquired defect of red/green discrimination no matter what disease has damaged the optic nerve. Compression of the nerve by a tumor, damage by inflammatory disease or toxins, and demyelinating diseases can all produce the same result. Just as the etiology of damage to the nerve is nonspecific, the location along the course of the optic nerve is equally indiscriminant. The ganglion cell fibers may be damaged in the anterior optic nerve or in the orbital or intracranial course of the nerve, resulting in the same acquired color vision defect.

The type of acquired dyschromatopsia caused by optic nerve disease seems to depend on the type of visual field defect associated with it. Köllner was again among the first to take notice of this phenomenon. The acquired red/green color deficiency associated with optic neuropathies is most pronounced in an eye in which the papillomacular bundle has been disturbed, producing a central scotoma with reduced acuity. Diseases that preferentially damage this part of the visual field include acute retrobulbar optic neuritis, tobacco–alcohol amblyopia, and Leber's hereditary optic neuropathy. However, not all optic nerve diseases result in red/green dyschromatopsias.

Generally, if acuity is spared by the insult to the nerve, a blue/yellow defect may predominate. Rare instances of traumatic optic atrophy causing damage to the peripheral visual field have been reported in association with greater deficits in blue/yellow discrimination. In addition, other primarily neuropathic diseases typically cause damage in the paracentral or Bjerrum region of the visual field. These optic neuropathies are also more commonly associated with blue/yellow hue discrimination defects. Glaucoma is the most common optic neuropathy to damage optic nerve fibers, causing a loss of the ganglion cell layer of the retina. The most common disturbances of the visual field in this disease are paracentral scotomas and arcuate defects in the Bjerrum region, while visual acuity remains undisturbed until the very late stages of glaucomatous visual loss. By far the most common acquired dyschromatopsia associated with glaucoma is an aquired deficit of blue/yellow discrimination.

The correlation first reported by Köllner between visual acuity and acquired hue discrimination defects provides a clue as to the possible pathogenesis of the altered hue discrimination in acquired diseases of the optic nerve and retina. For instance, it has become known that the visual field defects associated with these disorders have a characteristic topography that frequently allows one to distinguish between diseases of macular versus neural origin. Sparing of foveal sensitivity is a common feature of central scotomas produced by macular diseases. Inflammatory, degenerative, and toxic diseases of the macula frequently produce relative central visual field depressions that surround the foveal area in an annular pattern, while preserving an isolated mini-island of visual sensitivity located at the fovea. Macular edema is one of many retinal disorders that can produce a tritan-like (i.e., blue/yellow) acquired dyschromatopsia. Similarly, chloroquine retinopathy, which can also produce a tritan-like dyschromatopsia before visual acuity is severely damaged, also often causes a perifoveal annular depression of the visual field, corresponding to a bull's eye target configuration of the macular pigment epithelium. The phenomenon of foveal sparing in relative central scotomas has not been found associated with visual field defects produced by diseases affecting the papillomacular bundle. This includes the visual defects caused by compressive, demyelinating, and vascular disorders of the optic nerve. In those cases in which the topography of the central visual field has been carefully studied by static perimetry, the results have been the inverse of those found in primary macular disorders, i.e., there appears to be a preferential destruction of visual sensitivity at the fovea with relative preservation of vision toward the edges of the central scotoma.

Occasionally one sees patients with acquired dyschromatopsias but with no apparent visual field defect or significant reduction in acuity. Examples include people with "recovered" demyelinating optic neuropathies, patients with early diabetic retinopathy, and those with the early stages of glaucoma (elevated intraocular pressure, ophthalmoscopically visible nerve fiber bundle defects and cupping of the optic disc). In such patients, who commonly show a tritan-like acquired dyschromatopsia, the absence of a visual field defect is more apparent than real. Careful perimetry will usually demonstrate a generalized though significant depression in sensitivity spread across the entire central visual field. Histologic studies of the optic nerves of such eyes in patients with glaucoma have shown extensive, diffuse nerve fiber bundle loss.

The color vision tests that are used for detecting and characterizing acquired dyschromatopsias, such as the sorting or arrangement schemes used in the Farnsworth-Munsell 100-hue and the Farnsworth D-15 panel tests, are actually tests of the central 2° of the visual field. The sizes of the color caps were chosen in part because this is the same area of the visual field that was tested during the original colortesting used to derive the CIE chromaticity diagram. Although consistent results are obtained for groups of normal trichromatic observers when using this area of the central visual field, it should be noted that the distribution of color discrimination in this region is not homogeneous. There are genuine, significant variations in the perception of color over a very narrow range close to fixation in normal eyes. The variation is most dramatically demonstrable as a foveal defect for the perception of blue light. This so-called small-field foveal tritanopia (which is manifest within the central 30′ of the visual field) is primarily attributable to the absence or relative paucity of blue cone receptors in the foveal cone mosaic. This is the anatomic basis for a dense scotoma for the perception blue light in the central 30′ of the visual field. Therefore, when normal observers look at colored caps having a diameter covering the central 2° of the visual field, they must (of necessity) be using the more peripheral portions of the colored test objects to make hue discriminations between blues and yellows. A visual field defect producing an annular depression at the periphery of this retinal region, such as is common in macular disease, should result in a disproportionately greater impairment of blue/yellow than of red/green discrimination. In addition, with foveal sparing there will be a relative preser-vation of visual acuity. Conversely, those diseases that preferentially destroy foveal function early in their course will produce central scotomas that result in poor visual acuity and a preferentially greater destruction of visual function in the most central portions of the foveal and

Table 6.5. Ophthalmic findings that draw particular attention to possible color vision deficits

Associated findings	Etiologic considerations	Diagnostic considerations and strategies
Slit lamp, opthalmoscopy, retroillumination of the iris, blond fundus	Albinism	Electrophysiology
Optic disc signs	Optic neuritis, vascular disease, toxicity, space-occupying lesion	Neurology consult, electrophysiology, imaging (MRI)
Hyperpigmentation	Tapetoretinal degenerations, luetic disease, pigment epitheliopathy, embryopathies	Electrophysiology, serology, consider fluorescein angiography
Pigment epitheliopathy	Stargardt's disease, cone-rod dystrophies or other tapetoretinal degenerations	Electrophysiology Fluorescein angiography, anomaloscopy
Specific macular signs: bull's eye target pattern, radial folds, retinal drusen, macular edema	Chloroquine toxicity, juvenile retinoschisis, macular degeneration, toxic disorders, photic damage	Electrophysiology Rheumatologic consultation, biomicroscopy of the fundus
Visual field loss: Central scotoma	Optic neuritis, macular diseases (e.g., Stargardt's disease), barbiturate toxicity, chloroquine, tobacco/alcohol amblyopia, benzene, ethambutol, lead, methanol	Electrophysiology, neurologic consultation
Concentric constriction of the visual field	Tapetoretinal degenerations, chloroquine, phenothiazine, salicylates, benzene	Rheumatologic, neurologic, and/or psychiatric consultations to consider changing current drug use

perifoveal retina. This would be expected to result in a disproportionately greater destruction of red/green discrimination than of blue/yellow discrimination, provided that some residual function has been preserved in the central 2° region.

Ophthalmic Signs Associated with Dyschromatopsias

Perhaps the most important clinical data for the evaluation of acquired dyschromatopsias are the results of threshold static perimetry of the central 10° of the visual field. This area is covered by programs 10-2 and 10-1 of the commonly used automated threshold static perimeters. Perifoveal depressions caused by macular disease are best found by static perimetric examination of the central-most portions of the visual field. Likewise, focal depression of sensitivity at the foveal center – associated with poor acuity and preferential loss of red/green discrimination – will be apparent. During slit-lamp examination, retroillumination will reveal defects in the iris pigmentation in cases of albinism; opthalmoscopy of the optic disc can aid in identification of inflammatory, degenerative, vascular, or mass lesions. Careful fundoscopy allows correct identification of pigment changes caused by inflammatory or inherited degenerations, as well as the retinal toxicity of chloroquine, cases of juvenile retinoschisis, or signs of phototoxicity (e.g., in sun gazers). These entities are summarized in ■ Table 6.5. In the differential diagnosis of neurosensory color vision disturbances, one should keep in mind that spectral absorption by the ocular media can produce significant dyschromatopsias. This effect is most commonly encountered in the short wavelength, blue-light absorption of a nuclear cataract, which can cause a luminance-dependant dyschromatopsia.

It is helpful to think of dyschromatopsias in association with clinical data from other parts of an ophthalmic examination, such as visual field defects, electrophysiological tests, and fundoscopy, as these often help to narrow the scope of the differential diagnosis. Of particular importance are the static perimetric findings for the central 10° of the visual field.

Conclusion

Dyschromatopsias, sometimes not recognized by the patient, often reveal the presence of disease processes at a time when other signs of a visual disorder are minimal. This is particularly true for maculopathies and optic neuropathies. The results of color vision testing can lead to the discovery of an occult disorder. Careful consideration of the history, signs, and symptoms of the problem assist the physician in choosing the most efficient approach to its diagnosis.

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Chapter 7

Electrophysiology

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Electrophysiological methods of examination involve the recording of bioelectric potentials that arise during the neural processing of visual information by the various elements of the afferent visual pathways.

Changes in the various types of electrical potentials allow conclusions to be made about the locations and kinds of functional disturbances in the afferent neurons of the visual system. The examination methods of electrophysiology, including the electrooculogram (EOG), the various types of electroretinography (ERG), and the visually evoked (cortical) potentials (VEP) can be of significant help for the differential diagnostic classification of afferent visual disorders, when such conclusions cannot be made on the basis of morphological findings and subjective tests of visual function. The individual methods of examination have been standardized by the International Society for Clinical Electrophysiology of Vision (ISCEV, http://www.iscev.org/standards/index.html).

Anatomic Sources and Methods of Recording Electrophysiological Potentials

To make valid use the methods of electrophysiology it is necessary to have knowledge of the anatomic origins of the various potentials, the appropriate stimuli to evoke them, and the methods for recording and measuring their responses.

■ Table 7.1 gives an overview, arranged according to the various anatomic structures of the visual pathway. Nearly every part of the visual pathway can be studied with at least one electrophysiological method.

In the following pages, the methods of examination listed in ■ Table 7.1 are described.

Electrooculogram

Definition

The **electrooculogram** measures a physiologic, electrical potential difference between the cornea and the posterior pole of the globe, with the cornea by convention being the positive pole. This so-called ocular resting potential is a physiological, transepithelial electrical potential that lies across the retinal pigment epithelium.

Under steady conditions of illumination the resting potential maintains a constant value, called the basis potential, but it will vary with changes in illumination. This change is a response of the retinal pigment epithelium to shifts in ion concentrations in the extracellular fluid of the photoreceptors, and the ionic changes are a result of the phototransduction process in response to illumination of the photoreceptor outer segments. During EOG testing, the recorded, light-dependant changes in the ocular resting potential require an intact functioning of the retinal pigment epithelium and numerous photoreceptors.

Resting potential changes during EOG testing are indirectly measured through a pair of skin electrodes fixed close to the canthi of the eyelids. The patient then looks in alternating fashion at one light and then another, separated by a visual angle of 40° and located in a diffusely illuminated Ganzfeld sphere. The turning of the eyes produces variations in the voltage differential measured at the canthal electrodes, and these varying potentials are continuously recorded. The amplitude of the varying potentials depends on the ocular resting potential (■ Fig. 7.1). The examination is usually done with the pupils fully dilated.

For clinical EOG testing according to Arden (1962), dark adaptation of the light-adapted eye results in a decay of the ocular resting potential, which reaches a minimum value in about 10′, the so-called dark trough. During sub-

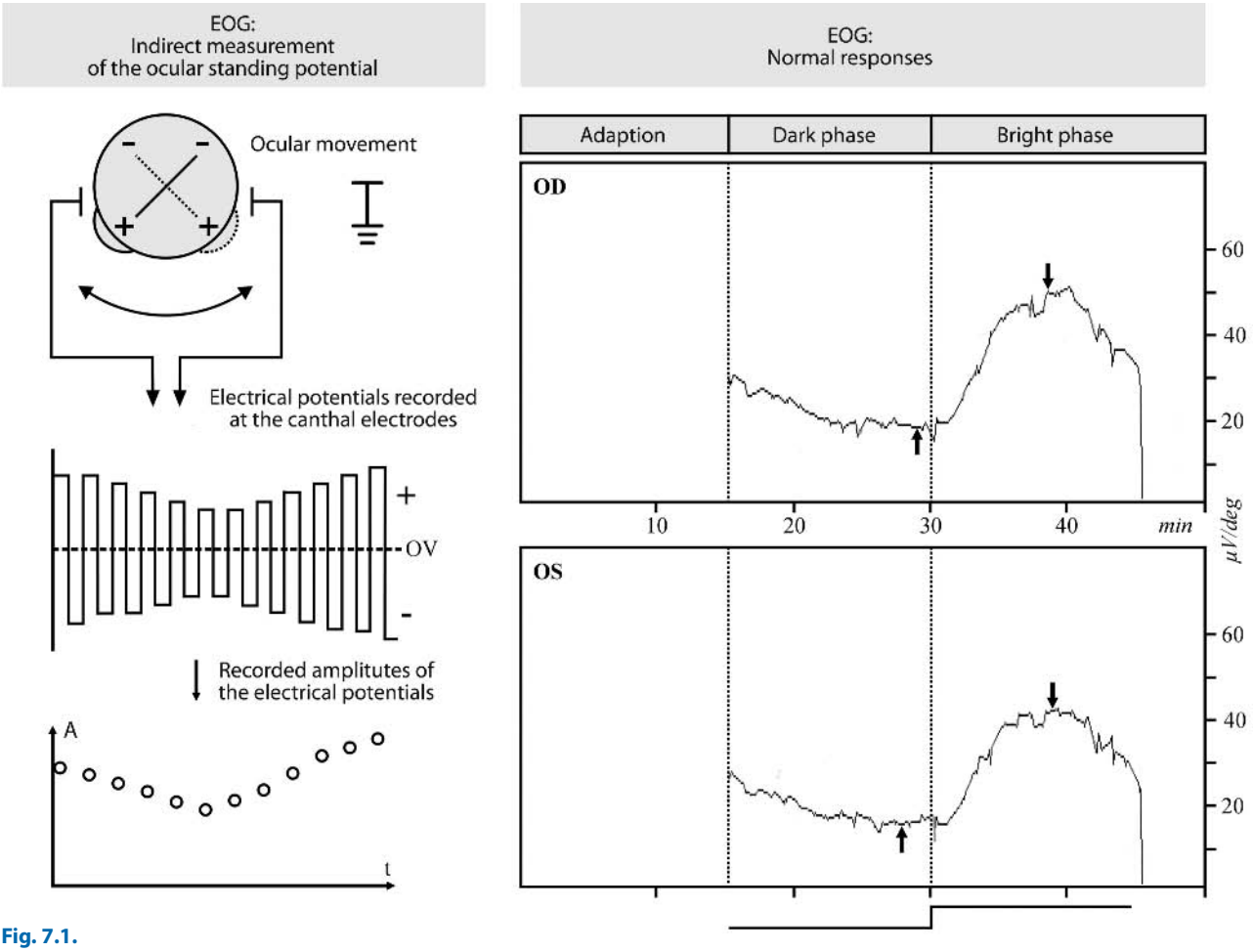

Fig. 7.1.

Table 7.1. Anatomic sources and methods of testing visually relevant electrophysiological potentials

Anatomic structure	Electrophysiological potential	Clinical test
Retinal pigment epithelium	Ocular resting potential	Electrooculogram (EOG)
Photoreceptor outer segments	Ocular resting potential	EOG
Rod outer segments	Rod a-wave	Scotopic flash electroretinogram (ERG)
Cone outer segments	Cone a-wave	Photopic flash ERG
Rod bipolar cells	Rod b-wave	Scotopic flash ERG
Cone bipolar cells	Cone b-wave	Photopic flash ERG
Müller's glial cells	Rod and cone b-wave	Scotopic and photopic flash ERG
Inner plexiform layer and especially amacrine cells	Oscillatory potentials	Scotopic flash ERG, with special filtering
Ganglion cell layer	N 95 potential sine wave–shaped potential	Transient pattern ERG Steady-state pattern ERG
Posterior pole, cones, bipolar cells, and amacrine cells	Local retinal potential tracings	Multifocal ERG
Retinocortical conduction time	Latency	Visually evoked potentials (VEP): pattern VEP, flash VEP
Primary visual cortex and the cone dominated portion of the afferent pathway (central visual field)	P100 amplitude, P2 amplitude	Pattern VEP, flash VEP

Fig. 7.1. The electrooculogram (*EOG*). *Left* The principles of the measure. As measured through cutaneous electrodes, gaze movements result in voltage changes around the eye that are continuously recorded. *Right* Normal findings of an EOG study. First, adaptation to room levels of light for 15′, followed by a dark adaptation phase with decay of the resting potential (*dark trough*) and then a light adaptation phase with an increase in the resting potential (*light peak*). The dark trough and the light peak are marked by *arrow heads* on the EOG tracing

sequent steady illumination of the eye, a continuous rise in the resting potential is evoked, which reaches the so-called light peak in 8 to 10′.

Pearl

The essential measure of the EOG is the ratio of the potential from the light peak to the dark trough, the so-called Arden quotient, which typically amounts to about 2.0.

Indications for Use of the EOG

Widespread damage to the pigment epithelial/photoreceptor complex results in a diminished Arden quotient, up to a complete loss of the light-induced potential rise. Disseminated retinal diseases of varying etiology affecting the photoreceptor layer can result in this kind of loss (■ Table 7.2). The flash ERG (see below) permits a differential judgment of the type of disturbance to retinal function, and is always recommended when there is a corresponding suspicion of retinal disease.

Table 7.2. ERG and EOG findings for various pathological conditions and symptoms

Disease	Scotopic ERG	Photopic ERG	EOG
Diffuse and regional choroidal degenerations			
Choroideremia	Markedly depressed or extinguished	Markedly depressed or extinguished	Markedly depressed
Gyrate atrophy	Markedly depressed or extinguished	Markedly depressed or extinguished	Markedly depressed
Diffuse choroidal sclerosis	Markedly depressed or extinguished	Markedly depressed or extinguished	Markedly depressed
Choroidal atrophy: central areolar, peripapillary, helical	Usually normal	Normal to subnormal	Normal to subnormal
Diffuse and regional photoreceptor dystrophies			
Retinitis pigmentosa (rod–cone dystrophy)	Depressed or extinguished scotopic ERG	Depressed or extinguished photopic ERG and prolonged implicit times	Depressed or absent
X chromosome RP carrier	Normal or depressed	Normal or depressed; implicit times often prolonged	Normal or depressed
Sector retinitis pigmentosa	Normal or depressed	Normal or depressed	Normal or depressed
Cone–rod dystrophy	Depressed	Depressed or extinguished	Depressed
Cone dystrophy	Normal	Depressed or extinguished	Normal
Achromatopsia	Normal	Extinguished	Normal
Blue cone monochromacy	Normal	Extinguished	Normal
Stargardt's disease – fundus flavimaculatus	Normal or depressed	Normal or depressed	Normal or depressed
Leber's congenital amaurosis	Usually extinguished	Usually extinguished	No reports
Pigment epithelium diseases			
Drusen, hereditary	Normal	Normal or subnormal	Normal or depressed
Sorsby's fundus dystrophy	Normal to depressed	Normal to depressed	Normal to depressed
Degenerative myopia	Normal to markedly depressed	Normal to markedly depressed	Normal to markedly depressed
Best's vitelliform dystrophy	Normal	Normal	Depressed to extinguished

Table 7.2. (*Continued*)

Disease	Scotopic ERG	Photopic ERG	EOG
Macular dystrophies			
Pattern dystrophy	Normal	Usually normal to subnormal	Normal to subnormal
Central areolar pigment epithelial (CAPE) dystrophy	Normal	Normal	Normal
Fenestrated sheen macular dystrophy	Normal to subnormal	Normal to subnormal	Normal to subnormal
Benign concentric annular macular dystrophy	Normal-subnormal	Normal-subnormal	Normal-subnormal
Vitreoretinal diseases			
X chromosome juvenile retinoschisis	B-wave depressed	Depressed	Normal
Goldmann Favre disease	B-wave depressed or extinguished	Depressed	Depressed
Syndromic disorders			
Usher's syndrome	Depressed to extinguished	Depressed to extinguished	Depressed to extinguished
Bardet-Biedl syndrome	Depressed to extinguished	Depressed to extinguished	Depressed to extinguished
Kearns-Sayre syndrome	Normal to extinguished	Depressed to extinguished	No reports
Myotonic dystrophy	Normal to depressed	Normal to depressed	Normal
Other hereditary diseases			
Albinism	Supernormal to normal	Supernormal to normal	Normal
Bietti's crystalline fundus dystrophy	Normal-subnormal	Normal-subnormal	Normal-subnormal
Presenting symptoms of nyctalopia			
Congenital stationary night blindness (CSNB), Riggs type	Depressed	Normal	Depressed
CSNB, Schubert-Bornschein type	B wave reduced	Normal to depressed	Normal
Oguchi's disease	B-wave reduced, delayed dark adaptation in ERG	Normal	Normal
Fundus albipunctatus	After prolonged dark adaptation, normal	Normal	Depressed
Melanoma-associated retinopathy (MAR)	B-wave reduced	B-wave reduced	Normal
Cancer-associated retinopathy (CAR)	Depressed to extinguished	Depressed to extinguished	Depressed to extinguished
Retinol deficiency	Depressed	Normal to depressed	Normal to depressed
Toxic disorders			
Chloroquine	Depressed	Depressed	Depressed
Thioridazine	Depressed to extinguished	Depressed to extinguished	Depressed to extinguished
Vigabatrin	Abnormal oscillatory potentials	Normal	Normal
Heavy metals	B-wave reduced-extinguished	Reduced-extinguished	Reduced

Table 7.2. (*Continued*)

Disease	Scotopic ERG	Photopic ERG	EOG
Inflammatory diseases			
Birdshot chorioretinopathy	Normal to reduced	Normal to reduced	Normal to reduced
Multiple evanescent white dot syndrome (MEWDS)	Normal to reduced	Normal to reduced	Normal to reduced
Luetic chorioretinitis	Normal to subnormal	Normal to subnormal	Normal
Rubella retinopathy	Normal	Normal	Normal
Retinal vasculitis	Normal to depressed	Normal to depressed	Normal
Circulatory disorders			
Carotid occlusion	Normal to depressed	Normal to depressed	Normal to depressed
Central retinal artery occlusion	Normal or reduced b-wave	Normal to depressed	Normal to depressed
Diabetic retinopathy	Normal or reduced b-wave and oscillatory potentials	Normal to depressed	Normal to depressed
Other causes			
Retinal or choroidal detachment	Normal to extinguished	Normal to extinguished	Normal to extinguished
Media opacities	Normal to reduced	Normal to reduced	No data

The EOG is the testing method of choice when the primary damage is thought to lie in the retinal pigment epithelium. The most important indications for the EOG are a suspicion of Best's vitelliform macular dystrophy and the suspicion of a pigment epitheliopathy, especially when assessing visual function during chronic chloroquine therapy.

Flash ERG

Definition

The phototransduction process in the photoreceptor outer segments, i.e., the transformation of a light stimulus into an electrical signal, and the further transmission of this signal elicits field potentials in various layers of the retina. In the **flash ERG** the potentials are excited by short flashes of light and detected by recording electrodes contacting the anterior surface of the eye.

Contact lenses, foil, or fiber electrodes are used for detecting the electrical potentials of the flash ERG. The fiber electrodes are most readily tolerated by children. As in EOG testing, recording is done with fully dilated pupils. A uniform illumination of the retina is obtained by having the patient positioned at a Ganzfeld sphere (a nearly spherical device with a neutral white interior finish much like that of a perimeter, and with a small port left open for access to the patient's eye) into which the light is flashed.

Depending on the level of light adaptation, the luminance of the surround, and the stimulus strength, a variety of time-based potential curves can be recorded. The Ganzfeld stimulus covers the entire retina, and the recorded responses are a summation of the electrical potentials generated by the entire retina – a mass response of multiple contributing potentials that are layered one on top of the other, and which are emitted by the various layers and cell types of the retinal neural network.

Note

Circumscribed, small area retinal lesions do not lead to measurable changes in the flash ERG.

A complete flash ERG according to the ISCEV standards basically includes records at two different levels of light adaptation:

1. During dark adaptation, i.e., with scotopic conditions, all records consist mainly of responses of the rod system, which is maximally sensitive in dim light or darkness (rod ERG and rod–cone ERG, ■ Fig. 7.2 a–c).
2. Subsequent recordings, done at fully light-adapted, i.e., photopic levels of illumination, comprise signals of the photopic cone system responding at daylight luminance levels (cone ERG, ■ Fig. 7.2 d, e).

In the ERG wave elicited by a single flash, one can identify typical components of the electrical potentials corresponding to various neuroanatomic structures. The two primary components, the a- and b-waves, are particularly clear and easily recognizable in an ERG response (■ Fig. 7.2 b) that was evoked by a strong flash of light in a fully dark-adapted eye.

- A-wave. A negative component arising at the beginning of the recorded response, produced primarily by the hyperpolarization of the photoreceptor outer segments. This response appears immediately after a strong light flash stimulus. The a-wave is only the leading edge of the negative potential contributed by the photoreceptors. Its further course is masked by the onset of the b-wave.
- B-wave. The b-wave arises from electrical activity in the inner layers of the retina, and is primarily generated by potassium currents that are liberated from the depolarizing bipolar cells during the neural processing of the photoreceptor input signals. Additional contributions to the positive b-wave currents arise from Müller's glial cells, which are oriented mostly radial to the vitreous body. The b-wave tests on one hand the integrity of the second neuron of the afferent path (the bipolar cell) and of Müller's cells, and on the other hand, it indirectly reflects photoreceptor function, since the activity of the bipolar cells is determined by the strength of the signal from the rods and cones. This explains why a reduction of the ERG a-wave because of photoreceptor disease also causes a reduction of the b-wave response. Conversely, there are retinal diseases that do not impair photoreceptor function or the a-wave of the ERG, but which selectively depress the b-wave because of damage to the inner layers of the retina, such as in retinal arterial occlusions (see below).

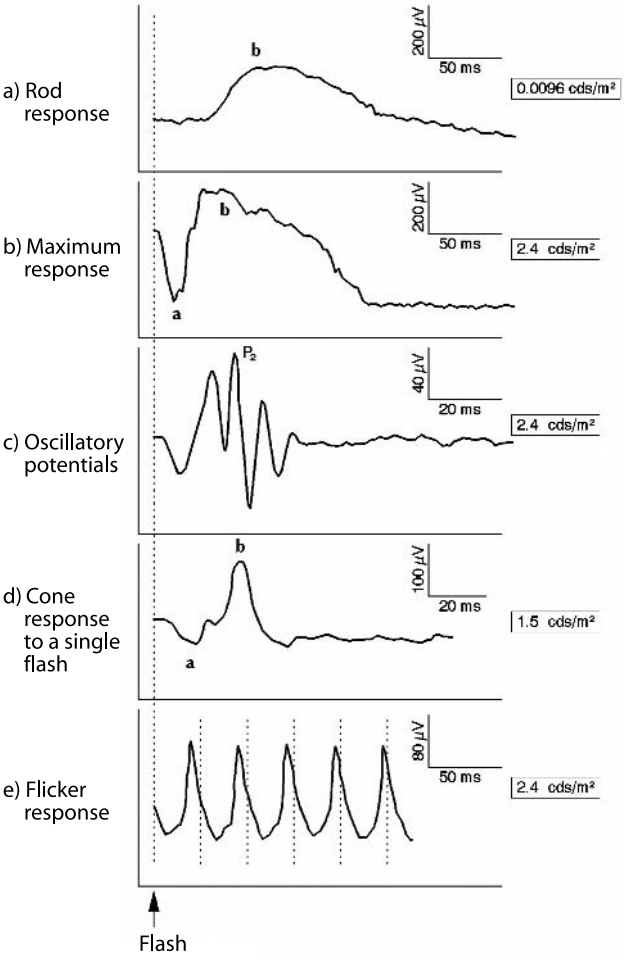

Fig. 7.2. Flash electroretinogram (ERG) **a** Dark-adapted isolated rod response to a flash of low intensity. **b** Dark-adapted rod–cone mixed response to a light flash of higher intensity (maximal response). **c** Dark-adapted oscillatory potentials. **d** Light-adapted cone response to a single flash. **e** Light-adapted cone response to a 30-Hz flickering stimulus. A- and b-waves as well as the second oscillatory potentials (P2) that are usually recorded are marked on the tracings

Rod ERG

If the dark-adapted eye is stimulated with a dim flash of light that lies below the threshold for cone responses, only rods with their maximally elevated sensitivity (a consequence of their dark-adapted state) will respond. This produces a pure rod ERG. At these weak stimulus intensities, the ERG response curves typically show no recognizable a-wave, since it is completely masked by the b-wave activity (■ Fig. 7.2 a).

Pearl

The density of rod photoreceptors is maximal at 15 to 20° of eccentricity, and is zero at the foveal center, which contains only red and green cones. The rod ERG response reflects (almost entirely) the function of the peripheral retina.

Rod–Cone ERG

Dark-adapted responses to higher stimulus intensities, as shown in ■ Fig. 7.2 b, are indeed rod dominated, but also contain a small contribution from the cone system. These are therefore called rod–cone responses, mixed responses, or maximal responses. Moreover, comparison of the tracings in ■ Fig. 7.2 a and b illustrate that with increasing stimulus intensity the amplitude of the b-wave also typically rises and its implicit time shortens. (The implicit time is similar to a latency; it is the time from stimulus onset to the peak of a response).

Oscillatory Potentials

A number of high-frequency voltage oscillations are typically found on the rising slope of the positive b-wave (see ■ Fig. 7.2 b), and they have been named oscillatory potentials. They are thought to arise from delayed responses coming of amacrine cells and horizontal crossed connections between the cells of the inner plexiform layer. These potentials are sensitive detectors of damage to the inner layers of the retina, whether in ischemic, toxic, or hereditary disorders. They can be isolated and recorded by special filtering of the ERG responses (■ Fig. 7.2 c).

Retinal ganglion cells make no detectable contribution to the flash ERG. A test that may be able to isolate ganglion cell function is the pattern ERG (see below).

Cone ERG

An isolated test of the cone system can be recorded when the eye is fully light adapted, i.e., under photopic conditions. The rod system is completely saturated and bleached at higher levels of light adaptation, and it does not contribute to the responses of the cone ERG. Isolated cone responses to bright single flashes of light resemble those of the dark-adapted responses to bright flashes in the rod ERG in that they include an a-wave, a b-wave, and a number of oscillatory potentials (■ Fig. 7.2 d). They are, however, different from the dark-adapted tracings in that they have smaller amplitudes and shorter implicit times.

Cone-specific responses can also be elicited with rapidly flickering light stimuli at a frequency of 30 Hz, since the rod system is not capable of responding to this high frequency of flicker stimulus. The ERG responses consist of a series of periodic, positive deflections of the tracings (■ Fig. 7.2 e).

The density of cone photoreceptors peaks to a maximal level within the macula, but the macula contributes little to the collective signals recorded by the cone ERG, since it has such a small area.

The flash ERG of cones shows changes only when caused by widespread, generalized photoreceptor degenerations, such as cone dystrophies, cone–rod dystrophies, and rod–cone dystrophies. With purely macular disease, it often shows no changes at all.

Pearl

For macular diseases, however, the multifocal ERG (see below) is a particularly valuable diagnostic test.

Evaluation of the Flash ERG

During the flash ERG, the following values are recorded:

- The amplitude of the a-wave, measured from the electrical baseline to the negative peak recorded just before the appearance of the b-wave
- The amplitude of the b-wave, measured from the valley of the a-wave to the positive peak of the b-wave
- The implicit times, meaning the time from the flash stimulus to the peak of the corresponding ERG peak

Reductions in amplitude or increases in implicit time are considered pathological when they deviate significantly from age-corrected normal ranges.

Indications for Flash ERG Testing

Given the above explanation of the physiologic and anatomic determinates of the ERG, the following are good indications of the need for ERG testing:

- *Inherited retinal dystrophies*. This group of disorders is the primary indication for flash ERG testing. These disorders cause a diffuse type of damage to the photoreceptor layer of the retina, with a consequent reduction in or complete loss of the amplitudes of both the a- and b-waves.
- *Nyctalopia*. Patients with night blindness commonly have associated and diverse hereditary and/or acquired diseases that contribute to a marked variation in prognosis. The ERG is a decisively helpful test when the differential diagnosis of a visual disorder includes heredofamilial retinopathies (see ■ Table 7.2).
- *Congenital nystagmus*. Nystagmus during infancy is frequently sensory in origin, meaning it is caused by a disturbance of retinal and/or retrobulbar disease of the afferent visual pathway. Retinal dystrophies as different from one another as achromatopsia, congenital stationary night blindness, and Leber's congenital amaurosis can be disguised by the presence of what appears to be a congenital nystagmus. The ERG plays a central role in

determining the diagnosis, since each of these diseases produces a characteristic change in the flash ERG.

- *Toxic disorders*. Siderosis bulbi, caused by a retained ferrous-metal foreign body, can be diagnosed in its early stages, typically by showing a reduction in the b-wave of the flash ERG. If the foreign body can be identified and removed from the eye, a remission in, or even reversal of, the visual loss may occur. Drug side effects, such as those of the phenothiazine group of agents, e.g., chlorpromazine or thioridazine), and the antimalarial drugs, e.g., chloroquine, can cause a depression of both a- and b-wave tracings in the flash ERG responses.
- *Chorioretinitides*. In this class of disorders, the ERG often shows little change. This aids in the ruling out of retinitis pigmentosa (RP) when inflammatory diseases mimic its fundoscopic appearance (so-called phenocopies of RP; see ■ Table 7.2).
- *Vascular diseases*. Ischemia in the retinal vascular tree depresses the oscillatory potentials of the ERG. In severe cases, ischemia can evoke a b-wave reduction with depression of the b/a amplitude ratios and a prolongation of the cone implicit times. ERG changes can be associated with various causes of retinal hypoperfusion, including diabetic retinopathy, central retinal vein occlusion or any of the occlusive inflammatory vasculopathies, such as Behçet's disease.
- *Clouding of the optic media*. In some cases where there is a loss of media clarity, whether by cataract or clouding of the vitreous, an ERG may be part of a preoperative evaluation, when interventional surgery is being considered. While it cannot establish a precise visual prognosis, it can give a coarse estimate of the preservation or loss of retinal function, ruling out a central retinal artery occlusion for instance.

Multifocal ERG

The multifocal ERG (mfERG), as developed by Sutter and Tran, has made it possible to derive simultaneously a local photopic ERG at each of a number of locations in the central visual field. This allows a topographic determination of ERG function within the central radius of 25 to 30° of the fundus. The summed potentials of the conventional flash ERG, by contrast, do not permit a localization of retinal disease. The stimulus used for the multifocal ERG consists of an array of hexagonal zones that interlock with one another and increase in size as the periphery of the central field is approached. The fields can be black or white and are positioned on a monitor or similar device, the center of which provides the patient with a fixation point. During the test, each of the hexagonal zones, independent of one another, change from black to white or vice versa. This is done in a pseudorandom sequence in which with each change of one of the test stimuli from black to white, a local retinal response is evoked. The recorded data are analyzed by means of a computed cross-correlation between the sequence of stimuli and the summed responses, and a calculation of the responses corresponding to each of the various stimulus areas is calculated. The measurements are recorded with conventional ERG electrodes. The amplitude of the local potentials can be plotted per unit area of the retina, i.e., they are displayed as a "response density" (■ Fig. 7.3 a). In this three-dimensional representation, the fovea with its high level of photoreceptor density is also the location with the greatest response density. At the left border of the display, the physiologic blind spot is seen as a local depression in the response density. Other choices exist for representing the local responses ("trace array" in ■ Fig. 7.3 c) or grouping and averaging of the responses according to their eccentricities relative to the fovea center. A final type of representation permits determination of the amplitudes and implicit times for each of the response groups during routine clinical use of the test.

Indications for the mfERG

The mfERG is particularly useful and indicated in cases where help is needed in the detection of retinal disorders confined to the macular and perimacular regions. It is a big diagnostic help at the very early stages of a macular dystrophy, such as Stargardt's disease (■ Fig. 7.3). In such early stages, there is often a significant discrepancy between a marked reduction in central visual function and a largely unremarkable appearance of the macula and optic disc. In addition, in cases of retinitis pigmentosa in its more advanced stages, when responses to the flash ERG are no longer detectable, the mfERG will often detect intact retinal function in a small area at the center of the visual field. This gives the physician an objective method for continued monitoring of foveal and perifoveal macular function.

Pearl

The mfERG is also useful for the topical classification of visual field defects of unexplained origin. If there is a suspicion that a prior choroidal infarct might have damaged the outer layers of the retina (which commonly causes no change in the fundus appearance), the mfERG can detect local zones of lost retinal function that correspond to the visual field defects.

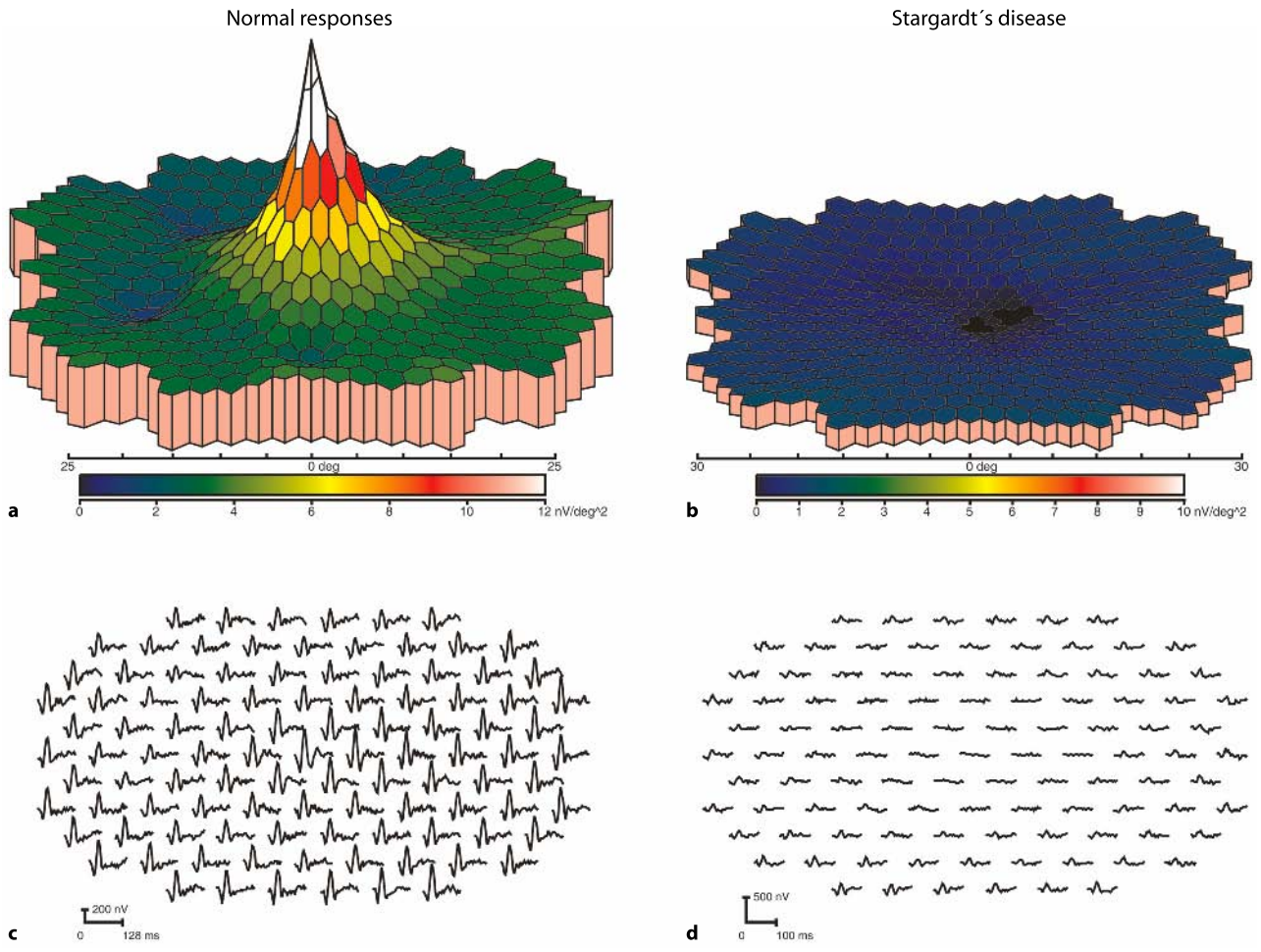

Fig. 7.3. Multifocal ERG (mfERG) of the left eye in a normal person (**a**, **c**) and a patient with Stargardt's macular dystrophy (**b**, **d**). **a** and **b** show three-dimensional and color-coded plots of responses. The patient with macular disease (**b**) shows an absence of foveal responses, the expected peak being replaced by a central depression of responses. **c** and **d** show the local response tracings in which the case of macular disease (**d**) shows an increasing depression of local response tracings that reaches a maximum at the foveal center. (Apfelstedt-Sylla, E., Gal, A. und Weber B.H.F.: Molekulare Grundlagen erblicher Netzhautdegenerationen: Retinitis pigmentosa, Zapfen- und Makuladystrophien. In: Handbuch der Molekularen Medizin [Eds.: Ganten, D., Ruckpaul, K.]. Springer, Berlin Heidelberg New York 2000)

Pattern ERG

Definition

The **pattern ERG (PERG)** measures retinal potentials that are responses to changes in a pattern reversal stimulus. The stimulus is most often a checkerboard pattern of black and white, displayed on a video monitor. The pattern is reversed (black squares become white and white squares become black) at a steady pace. The average luminance of the video monitor remains constant. The retinal responses are not to changes in total luminance, but to changes in the luminance of each square element in the pattern, so the retinal responses being recorded are contrast specific. The size of the squares can be changed, allowing the use of both coarse and fine patterns.

Measurements are made with fiber or foil electrodes, with the eye in an undilated state (normal pupil size and accommodation). For reversal frequencies of 4 Hz or less, the responses are said to be those of a transient PERG, while for frequencies of 5 Hz or higher, the responses are those of a steady-state PERG. The transient type of PERG forms a tracing initiated at each reversal of the pattern that has negative deflection at about 35 ms, a positive peak at about 50 ms, and another negative deflection that is maximal at about 95 ms (called the N95). The tracings of the steady-state PERG are similar in appearance to sine waves. The N95 values and the steady-state responses are thought to be contrast specific components of the PERG. Animal experiments have indicated that these responses are linked to events in the inner plexiform layer and the ganglion cell layer.

Indications for PERG Testing

The PERG is essentially suited to the detection of disorders that damage the ganglion cell layer of the retina, i.e., glaucoma and other optic neuropathies. It is ideal for the differentiation between the manifest visual loss of primary open-angle glaucoma on one hand, and ocular hypertension without visual damage on the other; its use has been adopted for many long-term clinical studies of glaucoma. From a clinically practical point of view, this method is too difficult to use in most office environments. Particularly for the very small patterns, reliable and reproducible PERG responses are difficult to obtain. This has made it impractical for every day clinical use.

Visually Evoked Potentials

The visual data processed by the neural network of the retina are passed on to the retrobulbar visual pathways through the axons of the ganglion cells, which form the optic nerve. The data are received by the neurons whose somas are located in the lateral geniculate body (LGB) and are passed on again in the axons of the LGB, which course through the deep white matter of the cerebral hemisphere, arriving at the primary visual cortex (also called the striate cortex, area striata, or Brodmann area 17) in the occipital lobe.

Definition

The **VEP test** measures field potentials that originate during cortical processing of the visual data received from the afferent visual pathway. On one hand, this electrical activity reflects the events of visual processing in the primary visual cortex, but on the other hand, it also reflects the integrity of all neural structures in the afferent pathway from the photoreceptor layer of the retina to the cortex of the occipital lobe.

The visual data originate essentially in the retinal cone system, because the VEP is conducted under photopic conditions of retinal light adaptation, and also because about one half of the visual cortex is devoted to processing data originating in the cone dominated region of the macula. The visual cortex is also located on the surface of the occipital lobe at the occipital pole, so that its activity makes up most of the responses recorded by the VEP.

The VEP can be elicited by simple flash stimuli (flash VEP), which is the method of choice for cases in which the patient is not cooperative. Most often, however, a pattern reversal stimulus is used, which is essentially identical to that described above for use in the PERG test. The patient fixes a visual target on the center of the pattern and an age-appropriate optical correction for near is used; the same as is used in threshold perimetry. The potentials originating in the occipital cortex are picked up by surface electrodes fixed to the scalp, relative to a reference electrode mounted on the brow or the vertex. The measured potentials are very small and are masked by much larger potentials that originate in the muscles of the scalp, and which are not related to visual function at all. Consequently, the same stimulus must be used 100 times or more, while summing the response tracings to produce a computation of average transients that have been generated mostly by events in the occipital cortex.

As in the use of ERG data, the VEP responses of importance are the amplitudes and implicit times of the recorded potentials. (Implicit time is measured from stimulus onset to the peak of a response.)

Depending on the stimulus configuration, various VEP tracings are recorded (■ Fig. 7.4):

- The flash VEP consists of a series of negative and positive peaks, whose amplitudes and latencies vary considerably between individuals. There is also an age-dependent effect. The latencies found in premature babies and infants are prolonged as compared with adults, and normalize with the maturation of the myelin sheaths of the visual pathway, completing the process at about school age. Frequently relevant response components include a positive peak at about 100 ms and a negative peak at about 150 ms (■ Fig. 7.4).
- In response to a patterned stimulus the VEP has a negative (N75), a positive (P100), and another negative (N135) component, where the number in the name is the average latency of the corresponding response peak. In routine clinical tests the P100 amplitude relative to the N75 valley and the latency of the P100 peak are determined.

The amplitude of the VEP in test subjects falls with a reduction in the size of the pattern elements (the squares of a checkerboard pattern) to a threshold value below which no responses can be detected. This threshold correlates well with the clinical values of visual acuity measured in the same subjects.

The pattern VEP amplitude as a function of a series of pattern element sizes can be used as an objective estimate of visual acuity.

Measures of the P100 latency are most frequently used, since it is a measure of retinocortical latency (■ Table 7.3).

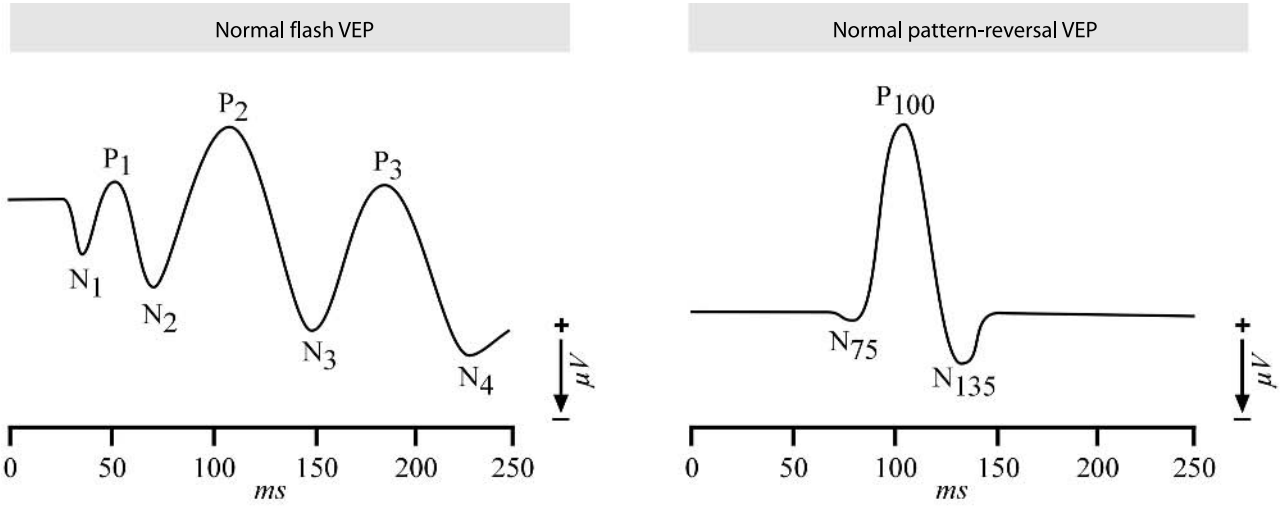

Fig. 7.4. Normal visually evoked potential (*VEP*) findings. *Left* A flash VEP tracing. N1–N4 mark the sequence of negative potential fluctuations. P1–P3 mark the positive peaks. *Right* A pattern-reversal VEP tracing with the clinically relevant P100 peak and both negative peaks N75 and N135 (modified from Harding GFA, Odom JV, Spileers W, Spekreijse H (1996) Standard for visual evoked potentials. Vision Res 36: 3567–3572)

Table 7.3. VEP signs in various disease categories

Disease	Amplitude	Latency
Optic neuritis	Normal to reduced	Markedly prolonged
Optic nerve compression	Minimally reduced	Moderately prolonged
Anterior ischemic optic neuropathy (AION)	Moderately reduced	Minimally prolonged
Leber's hereditary optic neuropathy	Reduced	Minimally prolonged
Dominantly inherited optic neuropathy	Minimally reduced	Normal or minimally prolonged
Papilledema	Normal or minimally reduced	Normal or minimally prolonged
Toxic optic neuropathies	Minimally reduced	Normal or minimally prolonged
Vitamin B12 deficiency	Normal	Minimally prolonged
Glaucoma	Normal or minimally reduced	Normal
Amblyopia	Normal or reduced	Normal or minimally prolonged

Most Important Clinical Uses of the Pattern VEP

Optic Neuritis

In optic neuritis, there is a destruction (demyelination) of the myelin sheaths of the ganglion cell axons, which causes a significant retardation in the velocity of neural conduction. Consequently, the P100 latency of the pattern VEP will, as a rule, be prolonged by 20 ms or more. The VEP is helpful when the clinical picture of an optic neuropathy is atypical for optic neuritis or the history and subjective findings are limited by poor cooperation, making the diagnosis uncertain.

In addition, the etiologic source of an existing optic atrophy can be retrospectively clarified. After (always partial) remyelination of a nerve damaged by optic neuritis, the prolonged latency will remain demonstrable for months or years. The VEP can also contribute to a diagnosis of multiple sclerosis in cases where a history of optic neuritis is lacking, since the majority of patients demonstrate prolonged VEP latencies, caused by asymptomatic demyelination, i.e., an episode of demyelination that was unnoticed.

Optic Nerve Compression

Compressive optic neuropathies can produce pathologic changes in the VEP in the form of diminished amplitudes of responses and prolonged latencies of responses. The VEP can thereby support the clinical suspicion of optic nerve compression, whether by tumors or by nontumorous space-occupying disorders such as in dysthyroid ophthalmopathy, during which swelling of the rectus muscles in the limited space of the orbital apex causes a compressive ischemia.

Objective Acuity Testing

As mentioned above, the response amplitudes and spatial frequencies of the pattern VEP, i.e., the objective resolving power of the visual system, correlates well with conventional, subjective measures of visual acuity. The pattern VEP can therefore objectively confirm an optical or neurosensory loss of visual acuity. Diminished pattern VEP amplitude, especially for small pattern sizes, can indicate the presence of developmental amblyopia.

Since the visual acuity of an amblyopic eye, as measured by grating resolution with the VEP, can be significantly better than that measured by subjective reading of optotypes, the VEP has been used for monitoring the clinical response to occlusion therapy only in cases where conventional measures are not possible. This can be the case in children with poor cognitive development for example. The objective estimation of acuity with the pattern VEP can also yield a higher value for acuity than that suggested by the patient's verbal responses. A measure of the "acuity VEP" can be in some cases of use during a certifying examination to measure the vision, when feigned or exaggerated loss of acuity is suspected. Similarly, purely functional reductions in acuity can be quickly identified in the setting of an outpatient clinic.

Indications for Use of the Flash VEP

The flash VEP requires neither cooperation nor steady fixation of the part of the patient. It can be used for infants and small children with uncertain visual function in order to test the intactness of the retinocortical sensory pathway. For example, it can be used to rule out or to confirm evidence of blindness in children with brain damage. In addition, it can be used to monitor visual development in small children.

In the setting of preoperative evaluation of media opacities, such as dense cataracts or vitreous hemorrhages, the flash VEP amplitude and latency are correlated with the maximal attainable acuity after surgical correction. The flash VEP findings can therefore be used to confirm the indications for surgery and the prognosis for successful improvement of vision.

Albinism

The afferent visual pathways of patients with oculocutaneous and ocular forms of albinism have a distinctive anatomic feature: A large majority of the fibers passing through the chiasm decussates to the contralateral side. This phenomenon can be detected with VEP testing through a comparison of the potentials evoked by monocular stimulation. The responses recorded over the contralateral occipital lobe are significantly larger than those generated by the ipsilateral lobe are. Given the usually distinct clinical picture of ocular and oculocutaneous albinism, the VEP is needed only in those few cases for which there exists significant uncertainty about the correct diagnosis.

Conclusion

The EOG measures the slow, light-dependent changes of the ocular resting potential. It tests the collective function of the pigment epithelium-photoreceptor complex. The most significant parameter is the Arden quotient. The most important indications for its use are in the diagnostic confirmation of Best's vitelliform macular degeneration and the monitoring of vision during long-term therapy with chloroquine.

The ERG measures the layer-specific summed potential of the retina and detects generalized or widespread retinal dysfunction. Changes in the a-wave mark disturbances of the photoreceptor layer; changes in the b-wave (with a normal a-wave) suggest a disorder in the region of the bipolar cell layer and in Müller's cells.

Oscillatory potentials are a sensitive detector of the function of the inner plexiform layer of the retina. The scotopic ERG measures primarily the intactness of rod function, and the photopic ERG isolates the function of the cone system. Important indications for use of the ERG include heredofamilial retinal degenerations, suspicion of a toxic retinopathy, inflammatory or vascular retinopathies, and retinal function testing in eyes with opaque media. In addition, the ERG is often decisive in the differential diagnosis of congenital nystagmus and nyctalopia (night blindness).

The VEP reflects the functioning of the cone-fed channel of the afferent visual system. Its most important clinical values are the amplitude and latency of the P100 response in the pattern VEP. In addition to providing an objective estimate of visual acuity, demyelinating, and compressive disorders of the optic nerve, testing of visual function and development in infants and small children, and suspicion of albinism are also indications for its use.

Further Reading

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Chapter 8

Optic Disc Signs and Optic Neuropathies

H. Wilhelm and U. Schiefer

The fundoscopic examination of the optic disc affords the physician one of the very few practical and completely patient-independent, objective neuro-ophthalmic signs.

Techniques and Criteria for Assessment of the Optic Disc

In the papilla of the optic nerve (i.e., that part that is visible to the physician – having a diameter of about 1.5 mm) about 1.3 million ganglion cell axons and their associated glial support cells crowd through the limited scleral opening at the lamina cribrosa to form the retrobulbar optic nerve (see Chap. 3).

Pearl

The optic nerve head (a synonym for the optic disc) is a sort of keyhole through which one has a direct view of the cells that make up the afferent visual pathway – including its intracranial segment as far as the lateral geniculate body.

There are numerous indirect, in part slit-lamp–supported, methods of fundoscopy that also give a stereoscopic view that improves the examiner's understanding of the in vivo anatomy of the optic disc. They provide an inverted virtual image of the living fundus. These methods, however, have not replaced the direct ophthalmoscope, which affords an erect image of the fundus that is 12 to 15 times magnified, allowing close inspection of the subtlest details. It requires mydriasis for its maximal benefit, but can be done at the bedside with no special requirements.

Note

Ideally, direct ophthalmoscopy should include use of a red-free light (i.e., with the green filter included in the light path). This method enhances the view of detailed features such as arteriolar, venular, and even capillary structures and the retinal nerve fiber layer. Pathological signs such as hemorrhages, traumatic folds, defects in the retinal nerve fiber layer, and the depth and location of optic atrophy are easily seen.

Photographic documentation of the findings (also including stereoscopic pairs and/or color filters, where applicable) is particularly useful for closer inspection of uncertain findings or for the monitoring of the patient's clinical course.

The following criteria should be included in the documentation of the optic disc appearance:

- The color of the optic disc
- The sharpness of the optic disc margin
- Any elevation of the optic disc
- The margin of the neuroretinal rim
- Cupping
- The apparent size of the disc
- The vessels on and near the disc
- The peripapillary region
- Any other distinctive features

Color of the Optic Disc

There is no single feature that determines a healthy optic disc appearance. A comparison to the contralateral disc and of the various segments within the disc is helpful. When judging the color of the optic disc, a number of considerations should play a role, including ametropia, papillary size, and hair and skin color: Fair-skinned, blond, myopic people with large optic discs have a lighter color to their discs, and vice versa.

Optic Atrophy

Definition

Optic atrophy as a feature should be differentiated between such types as very pale, chalk white, or profoundly atrophic nerves on the one hand and partially pale discs, with incomplete optic atrophy on the other. Specific forms of the latter group are *segmental atro-*

phies. Physicians speak of *simple optic atrophy*, when they mean that aside from the change in color, no other stigmata of disease are present, including cupping, notching of the neuroretinal rim, vascular changes, or anomalies. In speaking of *ascending atrophy*, one is referring to damage originating in the retina, while descending atrophy is the result of damage to the retrobulbar portions of the ganglion cell axons, comparable to classical Wallerian degeneration (see Chap. 3).

Retrogeniculate damage in the human is not manifested by any change in fundus appearance; the only exception to this rule is in infants and very young children, in whom damage to the retrogeniculate pathway can produce a trans-synaptic degeneration with resultant disc pallor.

The capillary bed of the surface of the optic disc is especially easy to see in red-free light, which causes the tiny vessels to contrast more sharply with the surrounding tissue elements.

! Note

Every case of optic atrophy, whether unilateral or bilateral, for which there is no known cause requires an imaging procedure to rule out occult disease. This can be either an MRI or a CT X-ray study.

Sharpness of the Optic Disc Margin

The nasal margin of the optic disc is commonly blurred or difficult to see. In addition, the disc margin at the superior and inferior poles is commonly obscured in part by the thick layer of healthy nerve fiber bundles arriving from the temporal retina and crowding into the narrow space at the vertical extremes of the disc margin. Only the temporal quadrant of the disc margin should always be expected to appear sharp. It is also generally true that small optic discs and/or the discs of strongly hyperopic eyes are usually not sharp. This is again due to the crowding of many healthy nerve fiber bundles into a tiny space. If the color is healthy, surface striations are visible, and there are no signs of hemorrhage, exudate formation or edema, blurred vision, or invisible disc margins need not be a cause for concern.

Optic Disc Elevation

An estimate of the prominence of the optic disc is easily made from the appearance in a stereo pair of photographs – quantification is possible with the direct ophthalmoscope with its high magnification and comparative shallow depth of field. If one at first focuses on the center of the macula and then on the papillary surface, the difference can be expressed in the dioptric power shift necessary to achieve focus. This is a rather accurate comparison of the relative focal distances to the macula and the optic disc surface. The reverse approach offers the risk of error, especially for younger observers with their ample range of accommodation. It is all too easy to exaggerate the difference when dialing in an increase in minus power to focus on the macula. Starting at the macula and adding positive dioptric power to focus on the disc minimizes the chance for error.

● Pearl

Rule of thumb: For any eye that is emmetropic, or nearly so, 1 mm of elevation corresponds to +3 diopters of change in focal length.

It should be noted whether the papillary elevation is segmental (as is seen in acute anterior ischemic optic neuropathy) or uniform in distribution.

Optic Disc Cupping and the Neuroretinal Rim

Conventional ophthalmoscopy allows only a qualitative estimate of the surface of the neuroretinal rim. The vertical cup-to-disc ratio (the ratio of the cup size to the diameter of the optic disc) allows only a semiquantitative assessment of the degree of cupping. Generally, this measure is usually higher in eyes with large optic discs, which are more likely to have a physiologic form of cupping (■ Fig. 8.1). It has been noted that this is particularly common in African-Americans, who with larger optic discs and large physiological cups, are at greater risk for visual loss to primary open angle glaucoma than do those with small cups and small optic discs. Small discs with small or no cups are also at risk, but can withstand higher pressures for longer periods without suffering glaucomatous loss of vision. Changes in cupping are indicative of damage, and even small increases in the cupping of small discs are cause for concern. Physiologic cupping is more likely to be horizontally oval and deeper in the nasal quadrant than in the temporal quadrant. More important than the size of the cup – which should be proportional to the size of the disc – is the appearance of the neuroretinal rim. Is it healthy in color? Are there notches in the rim, i.e., narrow zones in which the nerve fiber layer at the disc margin disappears? Locally circumscribed cupping, i.e., notches in the inner margin of the neuroretinal rim, are closely associated with glaucomatous optic nerve damage.

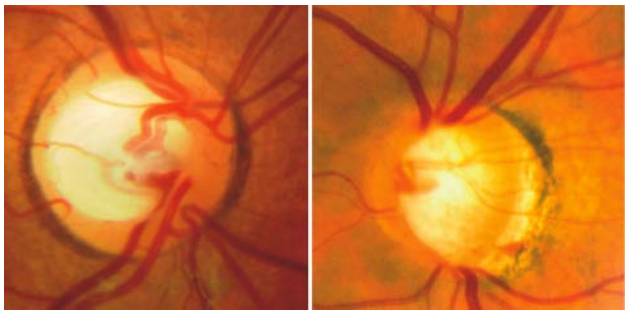

Fig. 8.1. Comparison of a large optic disc with a large physiologic cup (*left*) with a disc showing the pathological cupping of glaucoma (*right*). The anomalous disc has a preserved rim of healthy tissue that is widest at the inferior pole and most narrow in the temporal quadrant. In the glaucomatous optic disc this pattern is not seen, and the pathological cup extends all the way to the margin of the disc

Pearl

A helpful mnemonic is the ISN'T rule: The breadth of the neuroretinal rim is normally greatest at the *I*nferior disc margin, progressively narrower at the *S*uperior and *N*asal margins, and is narrowest at the *T*emporal disc margin. If this rule is not met, the examiner should consider that the possible presence of a pathological form of cupping is more likely.

A disc with no cup, frequently in combination with a smaller disc diameter, is thought of as a so-called disc at risk, as there is an association between this anatomical anomaly and the likelihood of suffering damage from anterior ischemic optic neuropathy (AION; see below).

Optic Disc Size

Similar to the color of the disc, the size cannot be quantitatively determined by conventional ophthalmoscopy. Blood vessels at and close to the disc can be used to provide a subjective comparison. (Vessels that appear to be too large for the disc are often a sign that the disc is unusually small, and vice versa.) In addition, any ametropia should be taken into consideration. Large eyes with axial myopia have discs that appear larger during direct ophthalmoscopy, whereas aphakic eyes have discs that appear smaller.

Large Retinal Vessels on and near the Optic Disc

Important observations of the major retinal vessels:

- Appearance of reflections of light at the vessel center (the so-called copper-wire appearance)
- Narrowing of arterioles
- Regularity of caliber, i.e., the relative sizes of arteries and adjacent veins (normally about 2:3)
- Notes relative to pathological changes at the crossings of veins by arteries

These are common and important signs of vascular disease, especially hypertension and diabetes. It has been observed that there is a close association between narrow retinal vessels and reduced rates of survival.

Very narrow, thready arterioles are typical in patients with tapetoretinal degenerations, and probably do not have the same prognostic significance.

Capillary ectasias (prominent capillary hyperemia) on and near the disc and obscuration of larger vessels at the disc margin (early sign of edema) are highly suspicious of acutely developing papilledema. Venous pulsations of the proximal retinal venous tree, usually at a sharp bend in the vessel as it turns into the lamina cribrosa, are an indication of normal intracranial pressure (ICP), but only if they are spontaneous. Visible, spontaneous venous pulses are useful when ruling out signs of elevated ICP, since their presence is a reliable indication of normal ICP, *if the intraocular pressure is normal*. However, an absence of spontaneous venous pulses neither confirms nor denies elevated ICP, since about 20% of healthy people have no visible pulsations. Also, note that venous pulsations can be elicited in most eyes by elevating the intraocular pressure, for instance with gentle pressure on the globe by the examiner's finger. Eyes with elevated intraocular pressure can exhibit spontaneous pulsations in the presence of elevated ICP.

Atypical vascular loops (corkscrew vessels) at the papillary border are occasionally misinterpreted as optociliary shunt vessels, when they are actually developmentally anomalous vessels. True optociliary shunts are a pathological sign of chronically elevated retinal venous pressure. They are thought to arise by means of a secondary enlargement or ectasia of preexisting vessels that allow shunting of the venous blood into the choroidal vascular bed, exiting the eye via the vortex veins. These shunts are common in eyes with optic nerve sheath meningiomas (see Chap. 12), but can also arise because of a central retinal vein occlusion, chronic papilledema, or compression of the anterior portions of the intraorbital optic nerve. In addition, shunts are known to form in eyes with distortions of the vascular tree, e.g., by epiretinal neuroglial membranes, in infants with retinopathy of prematurity, and retinal vascular sheathing as a feature of chronic inflammatory disease in the posterior segment.

All of the abovementioned entities can be seen more easily with the use of the green filter, i.e., in red-free light (see above).

Peripapillary Fundus

Of particular importance are nerve fiber bundle defects, as seen with red-free light or as photographed with blue light. Remember that the striations visible on the surface of the retina and optic nerve at and close to the margin of the disc are made up of more than a million axons per eye. What is seen, however, are not individual axons – they are too small, even with the magnified view of the direct ophthalmoscope. The striations are produced by bundles of axons with hundreds or thousands of axons needed to produce a visible stria. Hence, we speak of nerve fiber bundles.

Nerve fiber bundle defects can be present as an isolated finding or may be seen in company with local signs of pathological cupping of the optic disc. The striations are often invisible in an otherwise healthy eye in advanced stages of optic atrophy, in eyes with little or no pigment (blond fundus) or in elderly or highly myopic patients. Circumscribed, peripapillary choroidal atrophy with total loss of the retinal pigment epithelium (zone beta) or a peripapillary ring of irregular pigmentation (zone alpha) can also be a sign of glaucomatous atrophy or of prior bouts of inflammatory or vascular disease. Note should be made of any peripapillary infiltrates, exudates and/or hemorrhages.

Local ectasias of the posterior ocular wall are best seen with binocular methods of examination, but can also be detected with the direct ophthalmoscope by observing the planes of focus in and around the ectatic portion of the ocular wall. (The ectatic region will appear as an area of increased axial myopia). Remember the caution regarding younger examiners with large amplitudes of accommodation, so as to avoid false-positive findings (see above).

Other Distinctive Features

This group includes such features as tilting of the optic disc (oblique insertion of the optic nerve into the ocular wall) and anomalies shape or surface contour. The latter class includes drusen of the optic disc, which are often visible by either direct or indirect ophthalmoscopy (at the slit lamp) and with paraxial illumination (especially with blue light, which can demonstrate the fluorescent property of drusen). Further, epipapillary membranes, parapapillary folds and fundus reflex anomalies should be included in this category. An arc-shaped reflex (usually in the nasal quadrant) called Paton's line appears in conjunction with papilledema. This can lead in late cases to the formation of radial peripapillary folds and dispersion of pigment in the region of the papillomacular bundle.

Conclusion

Examination of the optic disc has a high standing among tests routinely done by the neuro-ophthalmologist. The transitions from normal to atrophic, edematous, or glaucomatous are fleeting. Close inspection with high magnification is necessary (i.e., with a dilated pupil and a direct ophthalmoscope) to properly judge the health of the optic nerve.

Further Reading

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Optic Disc Anomalies

Papillary anomalies are a frequent problem. It is necessary to differentiate them from such serious disorders as papilledema or atrophy. Commonly, the feature of concern is revealed as a harmless developmental anomaly, but such findings are no protection in themselves. The clinician must rule out pathological entities that can be misinterpreted as anomalous.

Summary of Optic Disc Anomalies

There are anomalies of the optic disc that are so characteristic that they can be diagnosed confidently, based on their ophthalmoscopic appearance alone. Among there are:

- Macropapilla
- Morning glory disc
- Tilted disc
- Coloboma of the optic disc
- Optic disc pit
- Persistent hyperplastic primary vitrous (the Bergmeister papilla)
- Myelinated nerve fibers
- Melanocytoma

More difficult to diagnose are:

- Micropapilla
- Optic disc hypoplasia
- Optic disc drusen

Macropapilla

Macropapilla (or megalopapilla, ■ Fig. 8.1) is a developmental anomaly marked by extraordinarily large optic discs with very large central cups and a narrow but healthy neuroretinal rim. They are typically bilateral, and optic nerve function is usually normal.

Pearl

Macropapilla is easily confused with advanced glaucomatous cupping, but is easy to distinguish from glaucoma by demonstrating the presence of a normal visual field.

In discs with very large cups that appear to be pathological, one should carefully examine the neuroretinal rim – that ring of tissue that surrounds the physiologic cup and covers the surface of the disc to its very margin. The examiner should take note of the color of the neuroretinal tissue (is it a healthy pink or is it pale, having no visible surface capillary bed). Are there notches in the rim with associated nerve fiber bundle defects? Is the thickness of the rim consistent with the ISN'T rule described above? Are there any flame-shaped surface hemorrhages? Do the retinal vessels kink or bend in a sharp angle as they cross the rim, or do they pierce the tissue without an abrupt change in direction? Large cups that are purely developmental often show the latter feature. The differentiation between a larger-than-usual disc and one that can be called macropapilla is not precisely defined. The size is not what is important, however; it is the presence or absence of signs of atrophy: death of ganglion cell axons. When the rim of a disc of this type is associated with an unrelated disorder, such as a tumorous compression of the retrobulbar segment of the nerve, the correct diagnosis can be much more difficult to determine. It is often necessary in such cases to use a neuroimaging procedure to rule out occult pathology, particularly if the patient has not previously been evaluated.

Morning Glory Optic Disc

The name morning glory disc has been given to a developmental anomaly of the optic disc that causes it to have an appearance that mimics that of an open flower of a morning glory vine (■ Fig. 8.2). It has a deep, central excavation filled with glial tissue that appears white to pink. The disc is also abnormally large and is nearly circular in outline. The vessels emanate from the margins of the disc, not from the center. They take a straight radial course as they move into the fundus periphery, simulating the trumpet-like opening of a morning glory. Other colobomas are usually not evident, but there is often an associated, trans-sphenoidal basal encephalocele. Affected children often have external signs, including a wide bridge of the nose, hypertelorism, and a cleft upper lip.

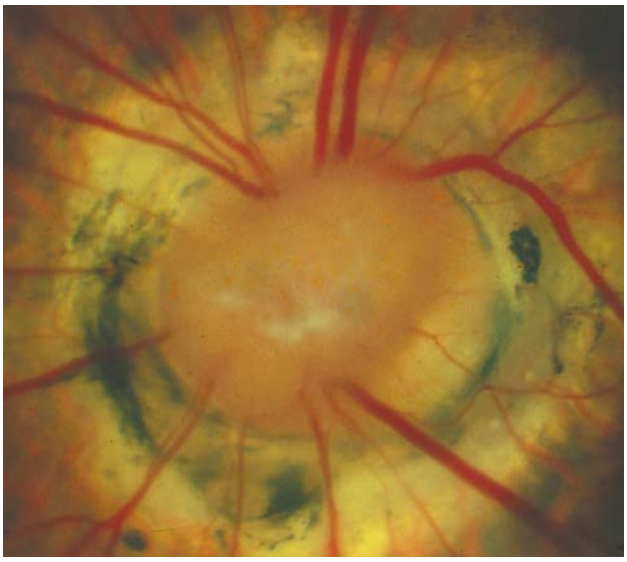

Fig. 8.2. Typical appearance of the morning glory anomaly. The optic disc is larger than normal and lies within a cone-shaped posterior extension of the globe that is filled with gray to pink-tinged glial tissue. The numerous vessels radiating from the disc are kinked at the disc margin, and disappear into the disc tissue close to the disc margin. There is a peripapillary zone of choroidal atrophy, and the pigment epithelial margin falls short of the disc margin

Visual function is often diminished to a variable extent, associated with macular edema, as also happens in the setting of an optic disc pit; there are in fact several similarities between the two developmental disorders. There is a report of a complication of retinal detachment repair in this setting: an intravitreal gas injection resulted in leakage of the gas through the disc and into the subretinal space.

Tilted Disc

The tilted disc is a minimal and harmless variant of incomplete embryonic closure of the optic cup (■ Fig. 8.3). It is most commonly tilted downward, so that the upper border of the disc appears elevated and the lower border appears flat and pale. Below the inferior border of the disc is often a crescent of choroidal atrophy, as if a coloboma had been present. The ocular wall is often ectatic in this region, and the retinal sensitivity is reduced, often producing a mild form of visual field loss in the superotemporal quadrant (refraction scotoma, see Chap. 4). Central acuity is not affected.

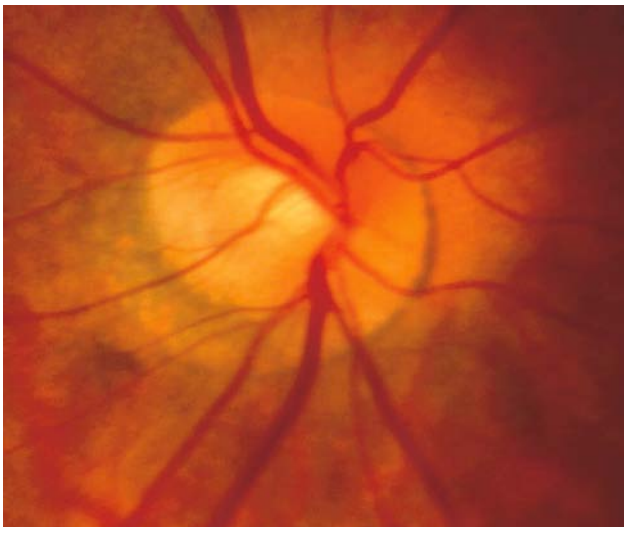

Fig. 8.3. The tilted disc. Inferiorly, there is a zone of choroidal atrophy (an inferior crescent). The cup emerges obliquely in the temporal direction. The nasal quadrant is elevated and pink, while the temporal quadrant is depressed and pale. The optic nerve enters obliquely into the globe. The appearance is most striking when seen stereoptically

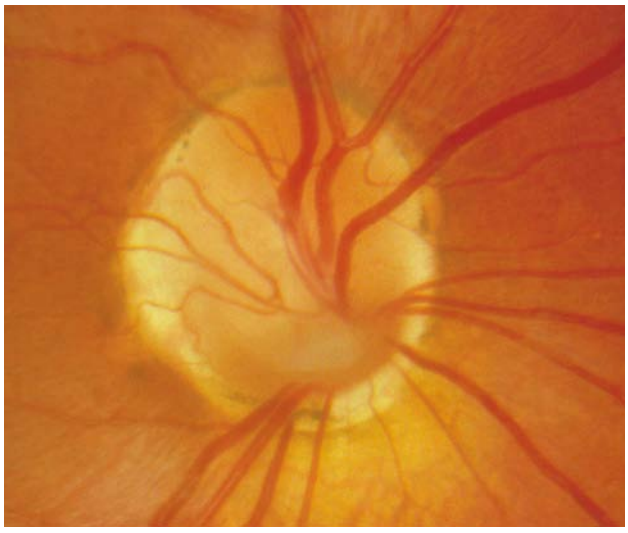

Fig. 8.4. Coloboma of the optic disc: Inferonasally (5 o'clock) there is a cleft in the disk. An entire sector appears to be missing. In this same region, the vessels are anomalously positioned. They dive into the disc in a pattern that closely resembles that of the morning glory disc. In addition, the nerve fiber layer is missing in the region of the coloboma, while it well preserved just above and below the coloboma sector. Inferiorly, the fundus pigmentation is noticeably weaker, a sign of an incomplete coloboma of the choroid

Coloboma of the Optic Disc

A coloboma of the optic disc is usually seen as an open excavation at the inferonasal border of the optic disc, a definitive sign of failed closure of the embryonic optic cleft (■ Fig. 8.4). Other colobomas (retina, choroid, iris) are common, and there is often an autosomal dominant pattern of a familial trait. In addition, hereditary (*PAX2* gene) is the association of optic disc coloboma with renal hypoplasia, called papillorenal syndrome.

Optic Disc Pit

Optic disc pits are also part of the spectrum coloboma-like developmental anomalies (■ Fig. 8.5). It is usually monocular and not associated with other ocular anomalies. It is thought to be a herniation through the lamina cribrosa into the subarachnoid space of the optic nerve. The visual acuity is usually normal, as long as macular edema has not developed. This latter complication was first described by Kranenburg. The pit can be very small, sometimes escaping attention until a careful examination with magnification detects its presence.

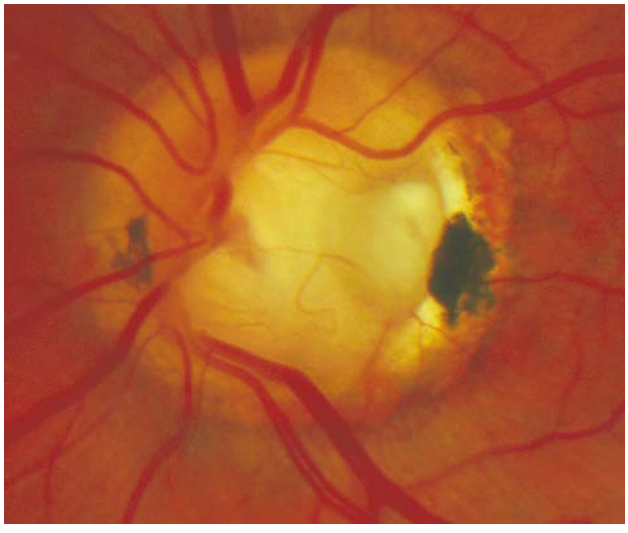

Fig. 8.5. A typical optic nerve pit, in this instance having already developed macular edema. The pit is located at the temporal border of the disc, while the remainder of the disc appears completely normal

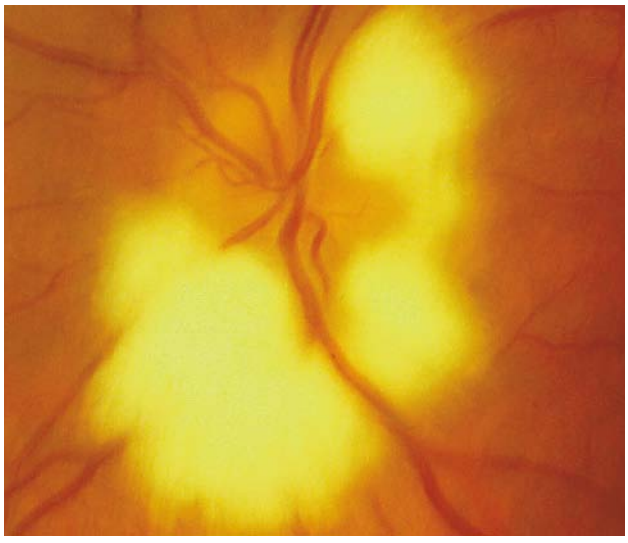

Fig. 8.6. Myelinated nerve fibers. The typical feathering of the margins is evident. This disc itself is difficult to judge, since it is in part concealed by the myelin and has an anomalous configuration

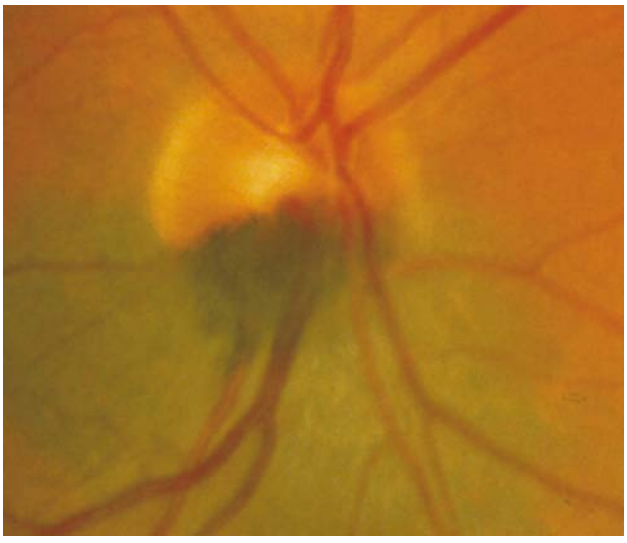

Fig. 8.7. Melanocytoma of the optic disc that spreads out into the inferior choroid. The color is very dark, and it has an indistinct border that reminds one of the feathering of myelinated fibers, even though an entirely different layer is affected

Bergmeister's Papilla: Persistent Hyperplastic Primary Vitreous

Remnants of the hyaloid artery can give the optic disc an unusual appearance. An epipapillary membrane of varying size rises into the vitreous cavity, often reaching all the way to the posterior lens capsule.

Myelinated Nerve Fibers

Myelinated nerve fibers of the retina are feather-edged, opaque, glistening white areas that obscure the retinal vessels beneath them (■ Fig. 8.6). These anomalies are usually present at the rim of the disc, as if they had been a continuation of optic nerve myelination that failed to stop at the lamina cribrosa. However, they can also appear separated from the optic disc by several disc diameters. Only in the immediate vicinity of the optic disc do they appear striking, and the more peripheral areas of myelination are easily confused with inflammatory exudates.

Pearl

The association of myelinated nerve fibers with cutaneous nevi is known as Gorlin's syndrome, and also as basal cell nevus syndrome, which needs to be identified early in life, so as to minimize the risk of developing cutaneous melanomas.

Melanocytoma

Melanocytomas of the optic disc are benign and require only regular follow-up examinations. They are strikingly black in color, prominent, and commonly extend across the margin of the disc or are surrounded by a choroidal nevus. The have a soft, feather-like surface appearance (■ Fig. 8.7). Differentiating these lesions from malignant melanomas is problematic in only a few cases. Their extremely black color is characteristic.

Micropapilla

Micropapilla is smaller than a normal optic disc. Its border, particularly in the superonasal and inferonasal margins, is blurred or even invisible, since the optic nerve fiber bundles are densely packed (a crowded disc). The cup is correspondingly small or absent. Visual function is normal.

Pearl

In some instances, a micropapilla can complicate recognition of glaucomatous atrophy, delaying the diagnosis of glaucoma. Also, enlargement of the cup in a very small disc should be recognized as more significant than a similar change in a larger disc. This type of change in micropapilla cases should lead to a careful study to rule out an occult form of glaucoma.

Optic Disc Hypoplasia

The most pathological form of a small optic disc is called papillary aplasia (■ Fig. 8.8). These discs have a pathologically low number of nerve fibers, in contradistinction to micropapilla, which has only a densely crowded but largely normal number of nerve fibers. The retinal nerve fiber layer appears thinned out. Around the papilla, there frequently is a region of atrophic choroid, which is about as large as a normal disc should be. Often, there is also an associated ring of pigment epithelium, in the center of which the actual optic disc is located. This pattern is referred to as the double ring sign. With a cursory examination, it is easy to assume mistakenly that the area of atrophy is the optic disc proper and to fail to appreciate the extent of the nerve fiber deficit. The hypoplastic optic disc has an easily demonstrable deficit in visual function. Of importance is an association of optic disc hypoplasia with midline defects of cerebral development (typically an absent septum pellucidum; see Chap. 19, ■ Fig. 19.9), which is referred to as DeMorsier syndrome. There is commonly an associated dysfunction of the pituitary.

An unusual form of disc hypoplasia is restricted to the upper half of the disc, a condition called altitudinal hemihypoplasia, which has been found in the children of severe diabetic mothers with a history of poor control of their diabetes while pregnant. The affected children have little or no visual field below the horizontal meridian, and commonly have a history of being "clumsy," i.e., frequently running into objects located below his or her line of sight. The child has no symptoms, as is typical for congenital deficits in visual function, and the dense loss of inferior visual field can be distinguished from the type caused by ischemic neuropathy or glaucoma, since the visual field defect of hemihypoplasia does not respect the nasal horizontal meridian.

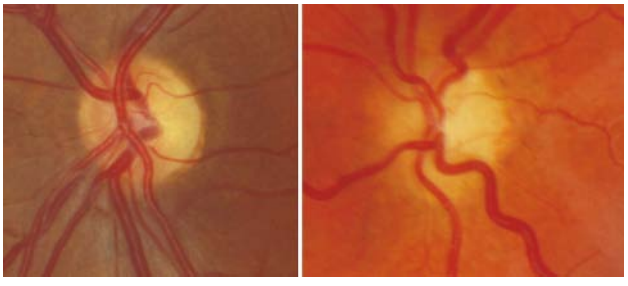

Fig. 8.8. Hypoplasia of the optic disc. The disc on the *left* has some healthy neural tissue and the nerve fiber layer is recognizable, allowing development of some visual function, while the disc on the *right* is almost completely aplastic. The latter eye has no light perception

Pearl

All children found to have hypoplastic discs in one or both eyes should be seen by a pediatric endocrinologist, and have an MRI done at least once to look for associated midline anatomic faults in brain structure.

Optic Disc Drusen

Definition

Optic disc drusen are (usually bilateral) hyaline bodies visible on the surface of the optic disc that are generally small, spherical in shape, golden in color, and have the properties of translucence and fluorescence. They are commonly a familial trait. Optic discs with drusen are usually smaller than normal (■ Fig. 8.9). Their appearance changes over the life of the patient. During childhood the drusen are commonly buried beneath the surface of the disc and can produce marked elevation of the optic discs with blurring of the margins that is occasionally confused with papilledema. Since papillary drusen can also be associated with hemorrhages at the border of the disc, or more commonly in the peripapillary subretinal space, the differential diagnosis can be very difficult. With maturation, the familiar appearance of drusen in adulthood develops its typical features.

Pearl

If one illuminates the disc with a bright ophthalmoscope or with a slit lamp and a 90-diopter loupe, and directs the light to one side of the disc, a form of sclerotic scatter will cause the drusen to light up from within, making them easy to see. This will occasionally cause buried drusen to become visible. With a blue filter in the light path, the drusen will also fluoresce. Often helpful is to photograph such discs at the camera used for fluorescein angiography and with the barrier filters in place. Autofluorescence of the drusen is then easily seen.

Drusen usually become calcified, which is of diagnostic help, since this makes them very prominent during B-scan ultrasonography (■ Fig. 8.10). This is an elegant and safe method of proof. In addition, calcified drusen can occasionally be seen on a CT scan of the orbit, when a layer of the scan happens to fall directly on the optic disc. The pallor frequently associated with drusen will cause the clinician to question the possibility of another cause, such as glaucoma, ischemia, or optic neuritis. Adding to the suspicion is a frequent appearance of arcuate scotomas, which appear along with visible nerve fiber bundle defects similar

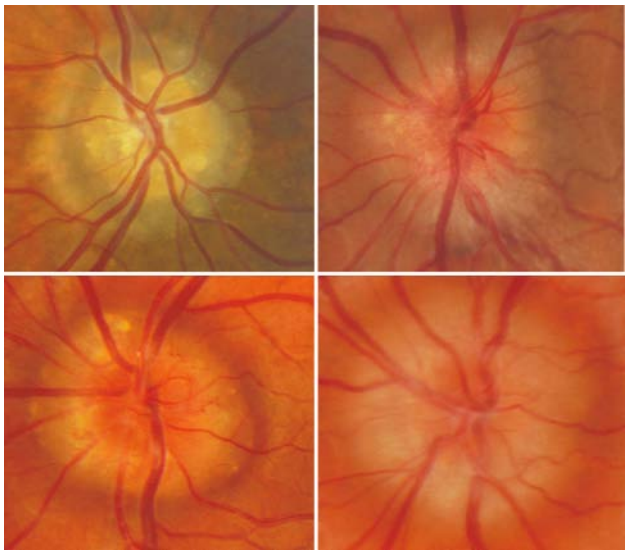

Fig. 8.9. Four examples of papillary drusen. *Top left* is an example of very characteristic features that are immediately recognizable. *Top right* and *bottom left* also are examples of visible drusen. In both cases illustrated in the *lower images*, one can also see subretinal hemorrhages in the circumpapillary zone. The *bottom right* example is not so easily interpreted, since it lacks the usual appearance. The drusen are buried deep within the disc tissue and can be demonstrated only by echography, photographs showing autofluorescence, or examination of other members of the patient's family

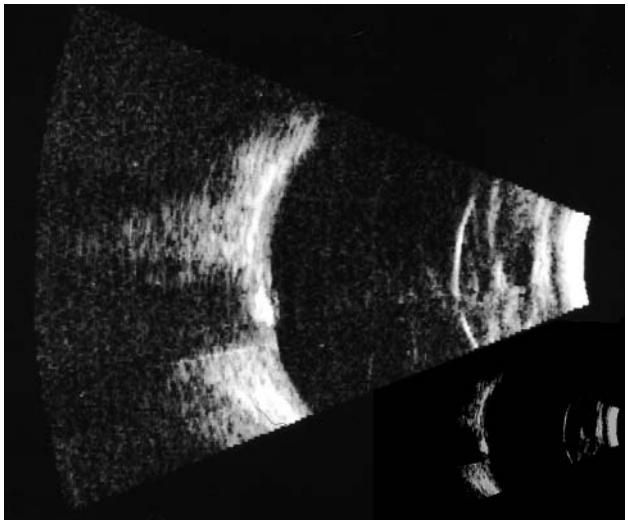

Fig. 8.10. B-scan echography of papillary drusen. The calcium deposits are easily recognizable and remain efficient reflectors of the ultrasound even when imaged with much lower levels of amplification (the *smaller image at bottom right*)

to those caused by glaucoma. The dominant inheritance pattern and strong familial tendency is very helpful in determining the correct diagnosis.

When there is a normal fundus appearance in these cases, ophthalmic ultrasonography with the B-scan instrument is very helpful at detecting buried drusen. When doubts about the diagnosis remain, even after all of the above tests, MRI scanning can be used. It is indicated when visual field defects progress or when other field defects develop that are not in a nerve fiber bundle pattern. (The drusen are not visible on MRI scans, but the purpose of scanning in this instance is to rule out other disorders). Disc drusen are common, and there is thought to be a significant number of cases that go unrecognized, particularly when they have not produced symptoms. The prevalence has been variously estimated at between 0.3 and 2.0% of the population.

Pearl

Since drusen are very common, one must always be on guard for a coincidental association of drusen with mass lesions, connective tissue diseases, optic neuritides, or any of a host of other causes of optic nerve disease.

Conclusion

The fundus appearance, visual function testing, examination of close relatives, and echography are usually sufficient to establish a diagnosis when evaluating a patient with an unusual or unexpected optic disc appearance. If the examiner is uncertain whether papilledema or optic atrophy can be ruled out based on fundus appearance and there are no historical data to indicate how long this fundus appearance may have been present, it is usually sufficient to follow the patient closely to ensure the absence of active, progressive disease. The schedule for monitoring should be appropriate for the suspected entity. If papilledema is suspected, the follow-up should be the following day, 3 days, 1 week, 1 month, and 3 months. If the level of suspicion is higher, or the examiner is truly uncertain about the diagnosis, an MRI scan will quickly rule out most of the disorders that threaten acute or chronic loss of vision. The physician must be familiar with these anomalies, their potential complications, and their associated findings.

Further Reading

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Papilledema

Definition

Papilledema is the (usually bilateral) presence of optic disc edema that has been caused by elevated intracranial pressure.

see also Animation 3.1

The pathogenesis of papilledema is not one of leakage of fluid into the interstitial spaces of the optic disc. It is actually caused by intrinsic swelling of the ganglion cell axons because of stasis of axoplasmic flow in the prelaminar optic nerve (see Chap. 3, ■ Fig. 3.3). This explains why atrophic optic discs cannot swell when intracranial pressure is elevated. If the disc swelling is present in one eye only, it still could be papilledema. Well-documented cases of unilateral papilledema have been described (see Huna Baron et al. 2001, in "Further Reading" below), and it is thought that the mechanism is one of sheltering the uninvolved eye from the elevated pressure due to an absence of the perineural subarachnoid space around the anterior portion of the optic nerve. This could be either developmental or acquired because of inflammatory scarring. The unilateral finding is rare, however, and when it is encountered, MRI scanning of the optic nerves is necessary to rule out other causes.

Initially, visual function is not disturbed by papilledema, although there is an enlargement of the physiologic blind spot. This is thought to be caused by a refractive scotoma, produced by elevation of the peripapillary retina, since the apparent enlargement can be reversed by using a hyperopic lens correction during the visual field testing (see Corbett et al. 1988, in "Further Reading" below).

Visual function is not initially harmed, but chronic papilledema (over months) can lead to a progressive gliosis and optic atrophy with loss of all useful vision.

Signs and Stages of Papilledema

Stage 1. Early stage of papilledema (■ Fig. 8.11): There is blurring of the disc margin and elevation of the disc in the nasal half. Capillary ectasias are visible on the surface of the disc, and the peripapillary nerve fiber layer has lost its clarity, consistent with the fact that the "edema" is intrinsic to the nerve fibers themselves. Small hemorrhages can be present.

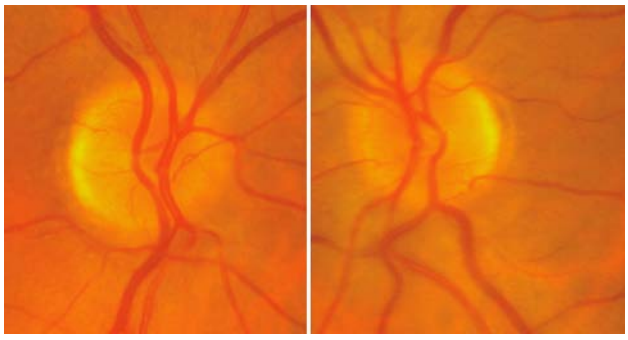

Fig. 8.11. Early papilledema in a patient with intracranial lymphoma. The signs are very subtle. They show only a mild loss of sharpness at the disc margin and early features of obscuration of the vessels by swollen neural tissue near the disc margin. When seen stereoscopically, the elevation of the disc was readily apparent. The diagnosis of early papilledema was later confirmed by the patient's clinical course

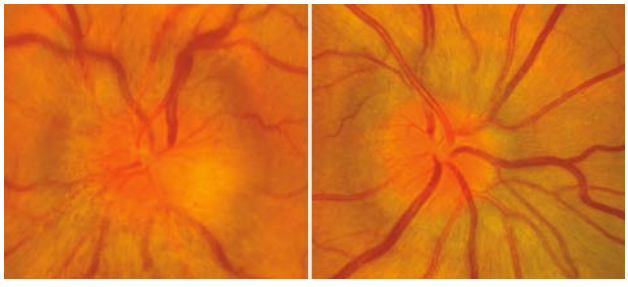

Fig. 8.12. Fully developed, acute papilledema in a 62-year-old man with an intracranial tumor; the appearance is asymmetrical, the swelling more easily seen in the *left image*, which is not uncommon for acute papilledema. Striking are the hyperemia and capillary ectasias on the surface of the disc and the obscuration of even the largest retinal vessels at the disc margin, again more apparent in the *left image*

Stage 2. Fully developed papilledema (■ Fig. 8.12): Elevation, blurring, and hemorrhages have worsened, and exudates are now visible. The physiologic cup is usually preserved.

Stage 3. Chronic papilledema (■ Fig. 8.13): The hemorrhages and exudates have subsided, being replaced by small glistening deposits. The physiologic cup has disappeared. Cilioretinal collateral vessels can appear at this stage. Small, concentric, retinal folds can appear in the peripapillary fundus (Paton's lines).

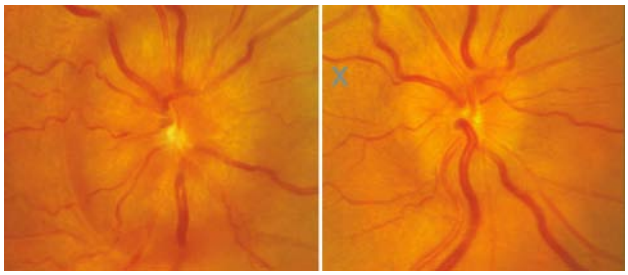

Fig. 8.13. Chronic papilledema caused by a sagittal sinus thrombosis. The *X* marks visible folds in the retina. Hyperemia and capillary ectasias have subsided. The cup of the disc is remains very small

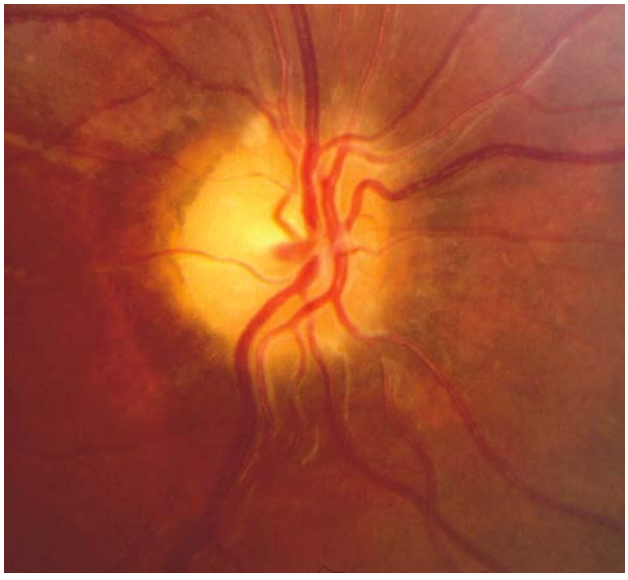

Fig. 8.14. Disc atrophy in chronic papilledema. The prominent blurring of the disc border and the vascular sheathing indicate that the problem is not one of primary optic atrophy

Stage 4. Atrophic papilledema (■ Fig. 8.14): The disc has become pale, although the margin remains more or less blurred, and the retinal vessels show sheathing.

Pearl

Spontaneous venous pulses are an important diagnostic criterion. It is always absent in the presence of papilledema. If it is visible, it is a reliable sign that intracranial pressure (ICP) is normal. The presence of venous pulses is a good sign, since it rules out elevated pressure *at the time of the examination*, but it does not exclude the possibility of there being intermittent elevations in ICP. The absence of spontaneous venous pulses is of no help, since at least 20% of healthy people do not show venous pulsations.

Visual function in the first two stages is unaffected, aside from the reversible enlargement of the blind spot. Loss of function is common in chronic papilledema and is often complicated by a maculopathy in addition to the optic neuropathy (see below). The macular changes are thought to be the result of traction of the retina, caused by the elevation and scarring of the peripapillary retina. Atrophic papilledema, by definition, is associated with severe and irreversible damage to the nerve.

Causes of Papilledema

Any elevation of intracranial pressure can result in papilledema whether by:

- Intracranial mass lesions
- Obstruction of the path of cerebrospinal fluid (CSF) flow by a mass, stenosis, or other cause
- Limitation of intracranial space by deformities of the skull
- Cerebral edema caused by tumors, inflammation or toxic disorders
- Increased rates of CSF production associated with tumors or inflammatory disorders
- Impaired outflow of CSF, e.g., caused by increased viscosity of the CSF, due to protein formation by a tumor or inflammation
- Elevated pressure in the venous sinuses that drain the CSF

In this connection, it should be clear that spinal tumors can be the primary cause of papilledema.

Note

Advanced stages of hypertensive retinopathy often produce optic disc edema. Marked narrowing of the arterial vessels should be a clue that the disc swelling could be caused by severely elevated levels of blood pressure. For this reason alone, a sphygmomanometer should be kept in every ophthalmic practice.

Clinical Management of Papilledema

Newly diagnosed papilledema should be considered an emergency. An imaging procedure should be done immediately (on the same day as discovery). Ideally, this should be done with MRI. Documentation of the pupillary findings, oculomotor function, and visual field examination should be completed as soon as possible.

! Note

The use of long-acting mydriatics is contraindicated, so that intensive neurological monitoring of the patient's findings will not be impaired.

When a mydriatic must be used for adequate visualization of the optic disc, one should use short-acting drugs, such as tropicamide, while documenting the time of administration. Additional measures depend on the results of MRI scanning. If the scan appears normal, the next step is to do a lumbar puncture for collection of CSF and determination of the ICP. Lumbar punctures in the presence of papilledema are contraindicated when there is a pressure gradient between the intracranial and spinal subarachnoid spaces.

● Pearl

Recovery of the optic disc appearance after correction of the elevated intracranial pressure can take many weeks.

! Note

A child with hydrocephalus – of whatever cause – is threatened with blindness if chronic papilledema develops. All such children require regular ophthalmic follow-up examinations to monitor their fundus appearance.

Unique Nature of Pseudotumor Cerebri (Benign Intracranial Hypertension)

Each of these names is misleading at best. The term pseudotumor originated at a time when tomographic imaging of the CNS was not available, and there were no convenient or easy ways to rule out the presence of a tumor. The second term suggests that the condition is harmless, which it is not. An alternative name is becoming more widely accepted: idiopathic intracranial hypertension, or IIH.

: Definition

Idiopathic intracranial hypertension (IIH) is understood to mean an elevation of ICP, with a normal-appearing brain on tomographic study (preferably MRI) and normal CSF. Elevated pressure is defined as a measurement in the recumbent position with values over 220 mm H_2O. The CSF must otherwise be normal. If protein levels are elevated (even slightly) or there is a pleocytosis, the diagnosis of IIH is inappropriate.

It is an open question whether by this definition one should accept elevated CSF pressure and papilledema associated with thrombosis of a cerebral venous sinus as a type of IIH, or if a separate diagnostic category, such as secondary IIH, should be used. Venous sinus thrombosis is easy to miss, if one does not look specifically for it. Appropriate neuroradiologic consultation is recommended to be certain of the presence or absence of a thrombotic pathogenesis in this setting.

One can use the diagnosis of IIH if the MRI scan shows no sign of tumor, the intracranial pressure is measured at levels above 220 mm H_2O in the recumbent position, and there is neither elevation of CSF protein nor pleocytosis. The MRI images should show ventricular size to be normal or even smaller than usual (an important differentiation from internal hydrocephalus). There is frequently an associated empty-sella appearance, which is a nonspecific sign of (mostly chronic) elevated CSF pressure. The fundus examination usually shows signs of chronic papilledema. Most patients complain of headache (see Chap. 16), and many describe transient obscurations of vision, which are brief episodes (lasting seconds) of graying or loss of contrast in the vision of the most severely affected eye. Transient obscurations of vision are another nonspecific feature of chronically elevated CSF pressure. Frequently, and especially among children, there is a paresis of one or both abducens nerves, yet another nonspecific sign. (Horizontal diplopia is occasionally a presenting complaint). The most common clinical picture is that of an obese young woman in whom no cause can be identified for the presence of elevated CSF pressure: IIH (■ Table 8.1).

! Note

In the usual clinical setting of obesity, the patient should be informed about the association between body weight and elevated CSF pressure. Encouragement of weight loss is usually ineffective, but certainly does no harm. Occasionally, an extraordinary exception can be found. With weight reduction of 6% or more, the CSF pressure can be lowered in obese patients with IIH. Reduction of pressure to a normal range is absolutely necessary in one way or another. The risk is one of developing progressive optic atrophy and binocular blindness. Also, macular edema can develop as a complication of the disorder, leading to a marked loss of acuity. There are no predictable time periods known to produce these complications, but the longer the disc swelling is present, the greater the cumulative risk.

Table 8.1. Signs, symptoms, and risk factors of pseudotumor cerebri

Without associated risk factors:	• Idiopathic (about 50%)
With known risk factors:	• Obesity (20%) • Pregnancy and postpartum period without sinus thrombosis (20%)
With suspected risk factors:	• Endocrine disorders (Addison's disease, Cushing's syndrome, corticosteroid withdrawal, hypothyroidism, hypo- or hyperparathyroidism, Turner's syndrome, adrenal adenoma) • Drugs (tetracycline, nalidixic acid, nitrofurantoin, penicillin, amiodarone, nonsteroidal anti-inflammatory agents, lithium, corticosteroids [both in high doses and on withdrawal]) • Hypervitaminoses (vitamin A at daily doses of 25,000 IU or more, vitamin D) • Associated hematologic disorders (chronic myeloid leukemia, polycythemia, iron deficiency anemia) • Other systemic diseases (lupus erythematosus, chronic obstructive pulmonary disease, uremia, borreliosis)

Pearl

However, it is not only overweight women who develop this syndromic presentation. Children and adults of normal body weight can acquire the same signs and symptoms as the result of exposure to certain medications and diets. Hypervitaminosis A, chronic use of corticosteroids, and chronic antibiotic use (e.g., daily use of tetracycline for treatment of pustular acne) are common associations. Particularly troublesome is the combined use of anabolic corticosteroids and supplemental vitamin A by competitive weight lifters.

Aside from venous sinus thrombosis, specific disorders associated with IIH are so uncommon that additional diagnostic study is not needed. Sinus thrombosis should always be suspected, however, and specifically ruled out. It is potentially a life-threatening disorder, and its correct management requires intervention with anticoagulants.

There are two basic options for managing the elevated CSF pressure, drug therapy, and surgical intervention. Medications known to be of benefit are primarily carbonic anhydrase inhibitors (e.g., acetazolamide), and diuretics (e.g., furosemide). Corticosteroids have been used, but are problematic in obese patients and are known to contribute to the risk in many patients. Surgery to lower CSF pressure in the setting of IIH in most instances should use a shunting procedure. Surgical intervention is helpful when drug therapy fails, and there is a strong element of pain in the patient's symptoms. If pain is not a problem, but the optic disc shows signs of impending visual loss, surgical fenestration of the optic nerve sheaths can reverse the papilledema and protect remaining vision. (Fenestration protects the ipsilateral eye only, often requires surgery for both eyes, as separate procedures, and does not lower the intracranial pressure.) Once a progressive gliosis of the nerve sets in, however, fenestration is not usually of benefit.

Note

Patients with chronic papilledema require regular ophthalmic follow-up examinations to monitor their vision (including careful perimetry) and to rule out signs of impending destruction of the optic nerve. The fundoscopic signs that are particularly important in this regard include numerous hemorrhages and/or extensive cotton-wool exudates. These should be recognized as ominous signs of ischemic damage. If the CSF pressure cannot be controlled quickly by medications, immediate surgical intervention should be considered.

Conclusion

Acute papilledema is an emergent problem that requires immediate attention, including an MRI scan, within 24 h of discovery. Evaluation should initially be focused on ruling out evidence of intracranial disease, such as mass lesions or internal hydrocephalus. If the scan is normal, the next step is a lumbar puncture to determine the CSF pressure and confirm normal CSF chemistry (no protein elevation, no pleocytosis). If these conditions are met, one is dealing with IIH. Management should then be focused on lowering the CSF pressure, whether by medical or surgical means, to protect vision by averting a potentially blinding optic neuropathy.

Further Reading

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Other Optic Neuropathies

The following group of the classic forms of optic neuropathy includes optic neuritis, ischemic optic neuropathy, compressive optic neuropathy (■ Table 8.2), as well as heredofamilial, toxic, metabolic, infiltrating, and radiation neuropathies. The optic neuropathies of glaucoma, drusen and other anomalies, including papilledema, are discussed in the earlier sections of this chapter.

Signs, Symptoms, and the Diagnoses of Optic Neuropathies

A patient with the recent onset of an optic neuropathy will most often complain of a sense of darkening and loss of color intensity in the affected eye. These symptoms often precede a loss of visual acuity. Unilateral disease is characterized by a relative afferent pupillary defect (RAPD), which is the most important objective clinical sign of optic nerve disease, as measured by the swinging flashlight test (see Chap. 2). Perimetry provides the next richest source of data for a differential diagnosis (see Chap. 4). Additional diagnostic studies are chosen after arriving at provisional diagnosis and a suspected pathogenesis. Most commonly, an MRI scan will provide the next most important data (see Chap. 20).

Optic Neuritis

Definition

Optic neuritis is an autoimmune demyelinating disorder of the optic nerve, being idiopathic, postinfectious, or as a component of multiple sclerosis (MS). It is less commonly associated with other systemic disorders.

Signs and Symptoms of Optic Neuritis

With an annual incidence of 5:100,000, retrobulbar optic neuritis (RON) is one of the most common optic neuropathies (■ Fig. 8.15). It is helpful to separate the cases into recognizably typical and atypical forms. The typical form meets the following conditions:

1. Usually unilateral
2. Acute

Table 8.2. Optic neuropathies

	Optic neuritis	Nonarteritic anterior ischemic optic neuropathy (NAION)	Optic nerve or chiasmal compression
Onset	Acute ~1 day	Peracute ~1 h	Chronic
Age group	<50 years	>50 years	No age-related difference
Pain	On eye movements	Mostly diffuse	More commonly headache
Optic disc, acutely	Normal or edematous	Always edematous (exception: PION)	Normal, edematous, or atrophy
Optic disc, chronically	Normal or atrophic	Sectoral or generalized atrophy	Normal or atrophic, rarely with persistent edema
Visual field	Nerve fiber defects, central scotoma, generalized depression	Arcuate nerve fiber defects, usually inferior altitudinal depression	Nerve fiber defects, central scotoma, generalized depression
General symptoms	Remitting and relapsing neurological deficits	Ischemic vascular disease	Possible endocrinopathies
MRI	Demyelination	Nothing unusual	Reveals mass
Therapy	High-dose corticosteroids or no therapy	Reduce risk factors	Surgical decompression, radiation, or no intervention
Prognosis, usual course	Substantial recovery	Little or no change	Benign tumors, visual recovery possible

PION posterior optic neuropathy

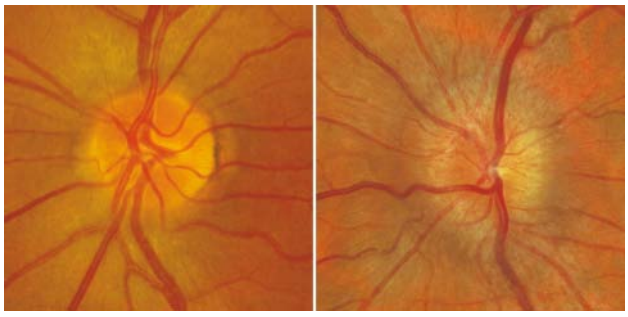

Fig. 8.15. At the acute onset of optic neuritis the optic disc can appear completely normal (*left*) or swollen

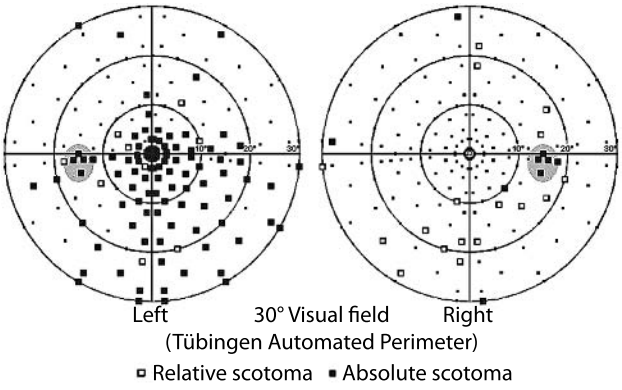

Fig. 8.16. The visual field in optic neuritis. In many cases, one finds a poorly defined central scotoma, in this instance affecting a left eye the defect extends inferiorly into the peripheral visual field

3. Age: in a majority of cases, 18 to 45 years
4. Pain on eye movement
5. Central scotomas or nerve fiber bundle patterns of visual field defects
6. Optic disc appearance normal or with mild edema
7. Tendency to begin recovery as soon as 2 weeks after peak visual loss at onset.
8. No evidence of systemic disease (other than MS)

This list is not meant to imply that cases of optic neuritis do not occur outside of these conditions, but these features are thought to be typical. Simultaneous, bilateral onset of optic neuritis is uncommon and suggests that some process other than demyelinating disease might be at work. In addition, in patients known to have MS, optic neuritis can occasionally appear as a slow, chronic process of visual deterioration. Such cases can also have an insidious onset, but are distinctly unusual in comparison to the above criteria.

Children are seldom struck by optic neuritis. When it does occur, a bilateral onset with bilateral optic disc edema is more typical in this age group. The bilateral pattern of onset is more frequent among children than it is among adults, but in absolute terms it is uncommon, hence, atypical. In addition, among children and older adults, optic neuritis can be the first manifestation of MS. Pain or dysesthesias are more likely to be associated with demyelinating disease than it is with other forms of optic neuritis. An uncommon, atypical form of neuritis is neuroretinitis in the absence of any history, signs, or other symptoms of demyelinating disease. This syndrome is most commonly the presentation of cat-scratch disease, for which the causative agent is usually *Bartonella henselae*. The presence of neuroretinitis almost completely excludes demyelinating disease as a causative factor.

Pearl

Pain on eye movement is very characteristic of optic neuritis and is reported by more than 90% of affected patients.

If the patient gives no spontaneous history of pain on eye movement, it is helpful to have the patient move through the cardinal positions of gaze, and then to ask whether this might have elicited discomfort.

The visual field loss at the time of presentation of optic neuritis has classically been described as a central scotoma (■ Fig. 8.16). While this is a common presentation, statistical analysis of visual fields gathered from large numbers of patients during the optic neuritis treatment trial (ONTT – a multicenter study on 455 patients) found that there is no typical visual field defect, and that any form of visual field loss could be found, including hemianopic, quadrantic, arcuate and para- or pericentral scotomas, as well as nonspecific, diffuse depression of sensitivity. When hemianopic defects that respect the vertical meridian are encountered, suspicion will fall on a possible tumor near the chiasm. The correct diagnosis is usually not a problem, however, since MRI scanning is commonly used during the study of both compressive and demyelinating forms of optic neuropathy.

The prognosis for vision in acute optic neuritis is largely favorable. The ONTT found that 1 year after the onset of an initial episode of acute optic neuritis, visual acuity of 20/20 was recovered in 70% of cases, and less than 10% of affected eyes had visual acuities of less than 20/40. Most patients recover nearly all of the lost acuity within about 5 weeks, and there is an additional period of up to a year after onset, during which small additional increments of recovery can be found.

Whether the optic disc is acutely edematous or not has no influence on the subsequent clinical course. Nevertheless, if atrophy is seen, the prognosis for visual recovery is not good.

Optic atrophy suggests that the neuritis is more chronic than acute. Either this presentation is a recurrence of an initially subclinical bout of neuritis or the onset of the

problem was not noticed by the patient. In the latter case, the physician should be concerned about the possibility of a compressive optic neuropathy.

Note

Optic disc edema is evident in about one third of patients with acute optic neuritis. It merely suggests that the site of damage is located in the anterior portions of the optic nerve. In the ONTT cases, however, it was found that some of the cases with disc edema were surprisingly associated with MRI evidence of inflammation located as far back as the intracanalicular portion of the nerve. The differentiation between papillitis and retrobulbar neuritis is purely descriptive, as far as the optic disc findings are concerned, and has no further meaning or consequence with respect to treatment or prognosis for recovery.

Additional Diagnostic Testing for Patients with Atypical Optic Neuritis

Definition

If the optic neuritis departs from one or more of the features described above, the episode should be recognized as **atypical optic neuritis**.

In cases with atypical features, the risk of a misdiagnosis is higher, and other systemic diseases are significantly more likely to be involved than in typical cases of optic neuritis. The history taken in such cases should include specific clarification of the following: fever, skin rash, arthritis, symptoms of pulmonary, renal, and/or cardiac disease. Significant clues include a prior diagnosis of rheumatoid disease (particularly systemic lupus erythematosus), sarcoidosis, borreliosis, and luetic disease. The last two entities are quite uncommon but will respond to antibiotic therapy, which makes their detection particularly important.

In all cases of atypical optic neuritis, an MRI scan is necessary. Aside from imaging of the nerve itself, the study should be done as it is in cases of typical demyelinating neuritis, looking for signs of disease in the deep white matter of the cerebral hemispheres (■ Fig. 8.17).

Additional Diagnostic Testing for Patients with Typical Optic Neuritis

No serological testing is needed when the case presentation is typical for acute optic neuritis. If the patient specifically wants to know the about the chances for future development of a more widespread demyelination, or when the discussion turns to consideration of the optimal treatment for early MS, an MRI scan is necessary.

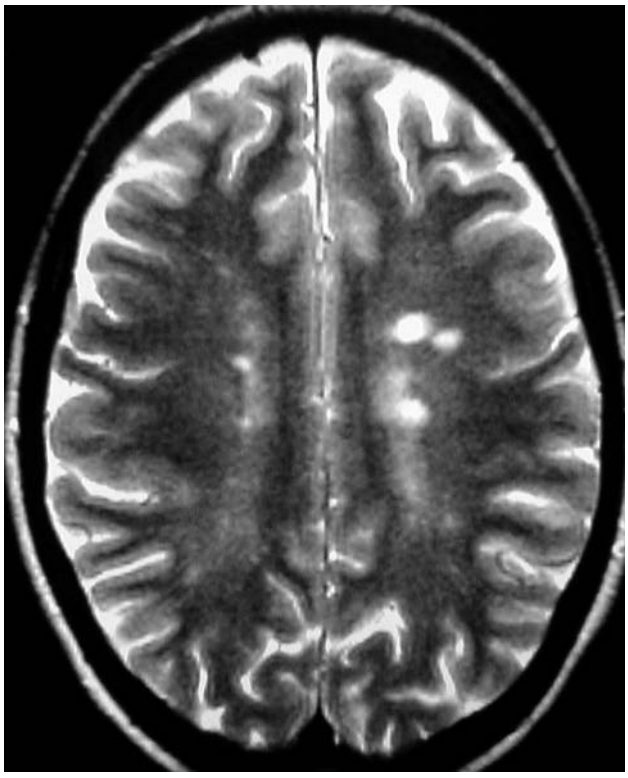

Fig. 8.17. MRI image of a patient with optic neuritis in the setting of known multiple sclerosis (MS): The typical, white foci of increased signal intensity in T2-weighted images mark the presence of large plaques of demyelination

Pearl

If the MRI shows at least one locus of probable demyelinating plaques, the risk of future development of clinically definite MS within the next 5 years amounts to about 50%. If the scan shows no such lesions, the risk is significantly lower at about 16%.

CSF studies can help to strengthen the validity of the diagnosis, but as a rule, serologic testing does not provide additional information that is any more useful than the information obtained by MRI imaging. When the diagnosis is uncertain, other tests, such as the visually evoked potential (VEP) or the flicker test of Aulhorn, can help to define a more focused differential diagnosis. In typical cases, however, they provide little in the way of useful information. It should be stressed that although the VEP is virtually always affected by demyelinating events (including prolonged latency and reduced amplitude of responses), it neither confirms nor rules out the diagnosis of optic neuritis. The diagnosis must always be defined by the clinical features that are found in each case.

Treatment of Atypical Optic Neuritis

The approach to clinical management of atypical optic neuritis depends on the probable cause of the neuritis. It is important to consider uncommon infectious disorders, such as borreliosis or luetic disease, since these require immediate treatment with antibiotics. Likewise uncommon, varicella zoster virus can present as an optic neuropathy or retinopathy, and such cases require early institution of intravenous acyclovir therapy. If an autoimmune disorder is the source of the problem, it should also be treated intensively with high doses of corticosteroids. It is commonly impossible to differentiate between idiopathic demyelinating optic neuritis and autoimmune vasculitis of the optic nerve, but both should be treated as early on as possible to protect vision. In cases of uncertain cause, it is often helpful to enlist the participation of a rheumatologist.

Treatment of Typical Optic Neuritis

The treatment of optic neuritis benefited substantially from the findings of the ONTT. The study's initial findings were first published in 1992, and subsequent long-term follow up has added additional, evidence-based improvements to our understanding of the disorder and its optimal management. Treatment is not indicated for the restoration of vision per se, since the prognosis for recovery of vision is favorable, whether with or without intervention. However, therapy does accelerate the rate of recovery and should always be considered in cases where the acute visual impairment is seriously disabling. If MRI scanning reveals one or more foci of demyelination, high-dose intravenous corticosteroid therapy can significantly delay the further development of signs and symptoms of MS in the subsequent 2-year period. Such treatment should always be considered in cases of optic neuritis that have no prior history of demyelination. The regimen consists of 3 days of intravenous methyl prednisone, 250 mg every 6 h for a total of 12 infusions, followed by 10 days of oral prednisone at 1 mg/kg of body weight per day. Alternatively 1000 mg of methyl prednisone are given in a single dose for 3 days.

! Note

Typical cases of recurrent retrobulbar optic neuritis (RBON) should not be treated with lower doses of orally administered medication, since this is known to double the risk of subsequent relapses of demyelination.

In the 1990s, the use of beta-interferon and copolymer 1 proved effective at reducing both the frequency and severity of attacks of demyelination in patients with clinically definite MS (meaning two or more separate episodes of demyelination). Another study reported in the year 2000 added additional impetus to our evolving understanding of MS and its optimal treatment. A post hoc analysis of the so-called CHAMPS (Controlled High Risk Subjects Avonex Multiple Sclerosis Prevention Study) found significant effectiveness of interferon beta-1a as a treatment for the first episode of demyelination, similar to the findings of the ONTT study. It specifically studied patients with an initial episode of RBON and MRI findings suggesting a higher risk for MS (nine or more T_2-weighted hyperintense lesions). When given weekly intramuscular injections of 30 μg of interferon beta-1a, the development of additional signs and symptoms of demyelination was reduced by 66%, as compared with placebo treatment, when maintained for a period of 3 years. The effectiveness of the treatment appears to be particularly greater for those patients having a more rapidly progressive course. Should one recommend such therapy for every patient with acute RBON and several foci of demyelination? The treatment is very expensive (more than $15,000 per year), and it its use has significant side effects in the form of flu-like symptoms, usually on the day of the injection and lasting into the following day. Currently, an informal consensus recommends that therapy be started after the first attack, if there is oligoclonal banding in the CSF, the MRI shows signs of subclinical demyelination, other causes of disease having been ruled out, and:

- A functionally disabling deficit is unresponsive to high-dose intravenous corticosteroid therapy for 2 months.
- Numerous (six or more) lesions are found on MRI scans of the brain.
- There are signs of active inflammatory activity in the white matter lesions (gadolinium enhancement or a distinct increase in the number of T2 lesions during a follow up period of 6 months).

This means that the ophthalmologist, when evaluating and treating patients with acute RBON, should discuss the risks of future additional neurological losses and the various therapeutic options for minimizing the risk. He/She can rely on the MRI as a rough indicator of elevated levels of risk, when recommending therapeutic intervention. These recommendations should be specific and clear, whether the patient's response indicates an interest in therapy or not. Patients with RBON and MRI signs of probable demyelination should be referred to a neurologist with experience in the treatment of demyelinating disease. In patients with normal MRI scans, or in those that do not wish to have further diagnostic study or treatment, such considerations are unnecessary. The optimal period during which immunomodulating treatment should be maintained is still unknown. Further studies of this issue are currently under way.

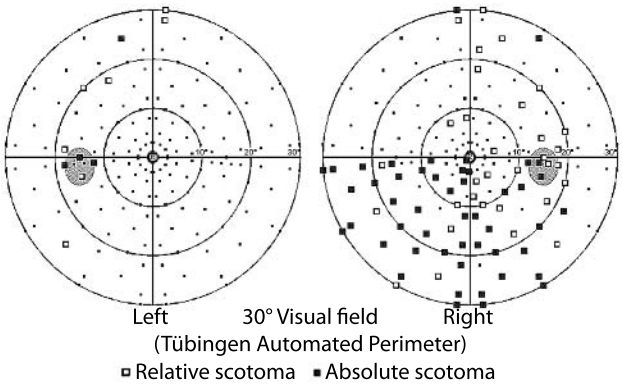

Fig. 8.18: The visual field in nonarteritic anterior ischemic optic neuropathy (NAION). A typical arcuate nerve fiber deficit in the lower half of the visual field in a right eye

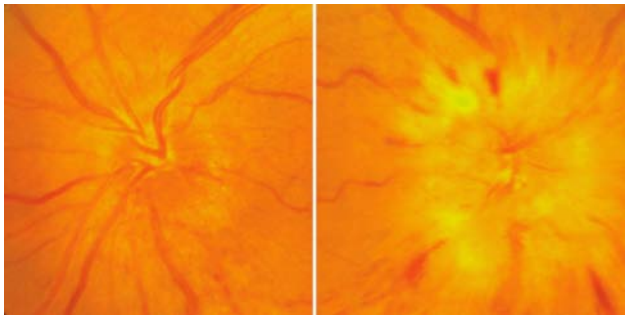

Fig. 8.19. NAION in the left eye (*right image*) with pronounced papillary swelling, hemorrhages at the disc margin, and exudates. Typical of one risk factor, the unaffected eye has a small optic disc with indistinct margins and no physiologic cup (the so-called disc at risk)

Anterior Ischemic Optic Neuropathy

Definition

Anterior ischemic optic neuropathy (AION) is characterized by the following triad: abrupt (usually monocular), painless loss of vision; optic disc swelling with or without surface hemorrhages and cotton-wool spots; and nerve fiber bundle defects in the visual field of the affected eye (■ Fig. 8.18). An important distinction must be made between the arteritic and nonarteritic forms of AION, in which systemic vascular diseases and local risk factors play a defining role.

Signs and Symptoms of Nonarteritic Anterior Ischemic Optic Neuropathy

The average age of patients with acute nonarteritic anterior ischemic optic neuropathy (NAION) is about 61 years. The visual loss occurs abruptly and without a prodromal warning, usually while the patient is asleep or within a 12-h period, and there is no associated pain or headache. The initial swelling of the optic disc subsides within 2 months, leaving a pale, atrophic appearance, which is often sectoral (most commonly located in the superior half of the disc). There is for the most part no or very little recovery of function. In about 10 to 20% of cases, there is one or more additional episodes of abrupt loss, in a descending staircase pattern, within the ensuing 2- to 3-week period after the acute onset. Later recurrences of loss in the same eye are very uncommon, but involvement of the contralateral eye can generally be expected within the subsequent 5-year period. As in other ischemic disorders, several risk factors play a role in the process. Aside from the association with systemic vascular diseases, chiefly hypertension and diabetes mellitus, morphologic anomalies of the optic disc are common. These discs are often rather small, having no physiologic cup (again, the so-called disc at risk; ■ Fig. 8.19), and fluorescein angiographic studies have found the affected discs are usually located in a watershed zone between two adjacent choroidal regions fed by separate branches of the short posterior ciliary arteries. The latter vessels are end arteries, i.e., they have no collaterals. With impaired function of the autoregulation of small-vessel blood flow, transient periods of systemic hypotension are thought to produce sufficient ischemia within the zone that includes the optic disc. The prelaminar portion of the optic disc, in turn, depends on the arterial supply of the peripapillary choroid. Relative ischemia that lasts for more than a few minutes can result in an infarction of the optic disc. This is thought to occur most commonly when the affected individual is asleep, i.e., when mean arterial blood pressure is at a minimum.

Treatment of *Non*arteritic Anterior Ischemic Optic Neuropathy

If there is no suspicion of an arteritic process (see below), a workup by the patient's internist or family physician should look for evidence of occult vascular disease. Aside from the usual risk factors (hypertension, hypercholesterolemia, and diabetes mellitus), the physician should also look for an elevated hematocrit, signs of a vasculitic process, sleep apnea, or heart failure. The younger the patient, the more intensive this workup should be.

Treatment in the acute phase of the nonarteritic type of ischemic neuropathy is not effective. Reduction in the alterable risk factors for the secondary prophylaxis of additional episodes is essential. Aspirin at a dose of 100 mg/day is thought to reduce the risk of contralateral involvement significantly during the ensuing 2-year period, and aspirin should be used if there is no contraindication. Hypercholesterolemia, hypertension, or occult diabetes should be

treated aggressively to forestall damage to the partner eye. The ophthalmologist making the initial diagnosis should immediately order studies of a complete blood count and determine levels of Hb_{A1c}, if the patient is not already known to be diabetic.

Signs and Symptoms of the *Arteritic* Form of AION

Note

It is particularly important to consider the possibility that an acute case of ischemic optic neuropathy might be arteritic in nature, for if the problem is indeed caused by arteritis, it should be considered as an emergent situation requiring immediate intervention with high-dose corticosteroid therapy.

The average age at the onset of anterior ischemic optic neuropathy in patients with temporal arteritis (AAION) is about 75 years. Arteritis can also present with branch retinal vessel occlusions, choroidal infarctions, or retinal ischemia, as indicated by the presence of numerous cotton-wool spots. Ischemic pareses of the extraocular muscles may be present, and ischemia of the scalp, sufficient to cause patchy areas of hair loss, have been known to appear. Even myocardial infarctions, hemispheric strokes, and cranial nerve palsies can be caused by severe forms of arteritic disease. Temporal arteritis (also called giant cell arteritis, cranial arteritis, or Horton's cephalgia [a now-obsolete term]) has the following typical signs and symptoms: headache, jaw claudication, scalp pain when combing or brushing the hair, malaise, fatigue, low-grade fever, anorexia, migratory myalgias, weight loss, and thickened, cord-like enlargements of the superficial, subcutaneous arteries of the scalp (■ Fig. 8.20). A commonly associated syndrome is that of polymyalgia rheumatica (PMR), which consists of giant cell infiltrations in the arteries of the scalp and chronic myalgias that require long-term use of low doses of corticosteroids. The risk to vision is thought to be much lower in PMR, and cases of acute temporal arteritis sometimes convert to the more chronic disorder of PMR.

Characteristically, AAION presents with a marked elevation in the erythrocyte sedimentation rate (ESR). Values commonly found are greater than 80 mm/h. In addition, C-reactive protein, leukocyte count, and alkaline phosphatase levels are elevated, while the erythrocyte count and hemoglobin levels are usually depressed. This occasionally raises the suspicion of an occult malignancy, leading to a fruitless search for tumors and a delay in the start of appropriate immunosuppression to protect vision from further loss.

In contradistinction to NAION, AAION is heralded by prodromal symptoms in the form of fleeting disturbances

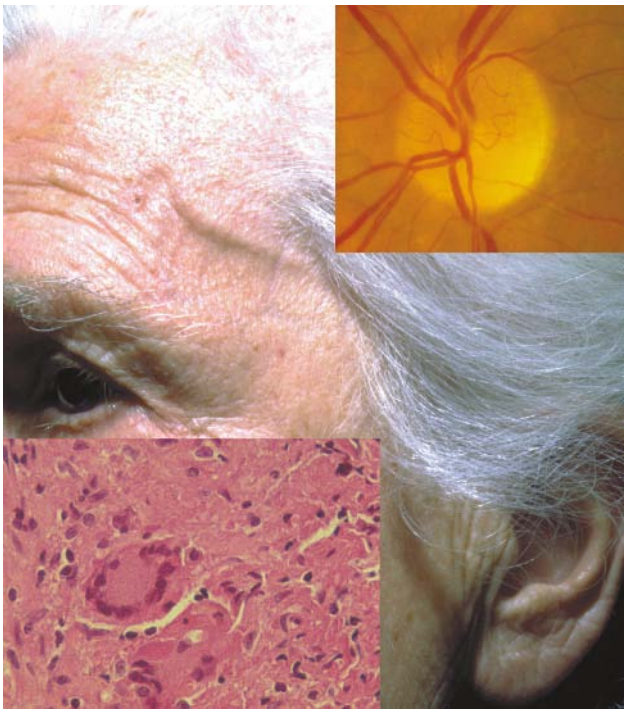

Fig. 8.20. Prominent branches of the superficial temporal artery, the histological appearance of a typical biopsy specimen with Langerhans' giant cells (by the courtesy of Prof. Dr. K.-P. Steuhl). Despite the marked drop in vision, the disc appears to have only a blurred margin and is minimal elevation. In such cases, a fluorescein angiogram will often reveal large areas of choroidal infarction

of vision. The optic disc is of normal size, and in the acute phase, it often appears already to have become pale. There are cases in which the fundus is initially normal in appearance, but then develops disc pallor within a few days, suggesting a posterior optic neuropathy (PION). Choroidal infarction is more common than thought. If there is a strong suspicion of arteritic disease, and the fundus is more or less normal in appearance, a fluorescein angiogram will typically show markedly delayed filling of the choroidal vessels, or even frank areas of complete choroidal infarction. In such cases, the electroretinogram (ERG) will show loss of the a-wave, caused by the infarction of photoreceptors that depend on the choriocapillaris for their oxygen and nutrient supply. The visual loss is often catastrophic, frequently blinding the affected eye completely, which is very uncommon in the nonarteritic NAION.

Pearl

All patients who are 50 years old or older, when presenting with ischemic neuropathy, should be questioned with a review of the common symptoms of arteritic disease. AAION in the presence of a normal ESR is very uncommon.

The diagnosis should be confirmed by biopsy of the superficial temporal artery and demonstration of the pathognomonic histopathology in the arterial wall. A positive biopsy is definitive proof of the presence of arteritic disease, but a normal-appearing vessel does not rule out arteritis. For this reason, a biopsy should be done only when the physician thinks there is a distinct probability of arteritic disease, and the biopsy should be used for confirmation of the diagnosis. This confirmation will frequently benefit the patient 6 months later, when the effects of chronic immunosuppression appear, and other physicians participating in the patient's care ask about the certainty of the diagnosis. The one condition that can most effectively mimic arteritic disease is end-stage atherosclerosis. In these patients, and in those with true arteritic disease, the temporal artery may be carrying blood as a collateral supply to the brain. Doppler echography of the carotid arteries and their branches can often help with managing such cases.

! Note

The desire for confirmation of the diagnosis by biopsy should never be allowed to delay the start of treatment. The pathognomonic signs in a biopsy specimen are often preserved for 2 or more weeks after the institution of high-dose corticosteroid administration. In untreated cases, involvement of the contralateral eye will occur in about one half of all cases, and the damage to the second eye is just as severe as in the first. One in seven patients will suffer loss in the second eye within 24 h of the initial loss, and it is not uncommon to encounter cases that have suffered bilateral loss of all light perception within a few days. The fresh diagnosis of this disorder constitutes a genuine ophthalmic emergency and requires the start of therapy immediately. Some practitioners keep a supply of prednisone tablets in their offices, so that the start of treatment will not have to wait until a prescription is filled.

Treatment of AAION

Treatment should be the immediate administration of a high dose of a corticosteroid. Prednisone is the most commonly used agent and should be given at doses of at least 1 mg/kg of body weight daily. There is no uniform agreement as to the optimal dose of prednisone, but while doses of 30 to 50 mg/day may be sufficient to relieve the general symptoms, they are inadequate for the protection of vision in the contralateral eye. There has been a trend toward the use of very high doses during the first day or two of treatment: prednisone 250 mg intravenously every 6 h. In patients with severe disease, consideration can be given to the use of heparin during the initial phase of treatment to lower the risk of intravascular thrombosis. When the ESR has been brought into a comfortably normal range, the changeover to oral prednisone is thought to be safe. Divided doses are important at this stage to avoid variations in blood levels of the drug that could allow recurrent progression of visual loss. A relief of symptoms and reversion of the ESR into a normal range give the signal for changing to a once-daily dosage of the oral drug, after which the dose can be gradually tapered from the initial 60 to 80 mg/day over a 6-week period down to the threshold of cushingoid side effects at about 10 mg/day. Patients should be instructed to report immediately any recurrence of the arteritic symptoms (headache, scalp tenderness, jaw claudication, myalgias, etc.).

Elderly patients with arteritic disease have a high level of sensitivity to the side effects of these drugs. Particularly important in the initiation of treatment with high-dose corticosteroids is the unpredictable complication of acute psychosis, which can be potentially life threatening. It is a good practice to admit patients to hospital for at least the first 24 h of therapy, so that a complication of this sort will be noticed. Routine testing of the blood levels of glucose and electrolytes is always indicated. Prophylaxis for the prevention of osteoporosis and/or gastric ulcer is always indicated as well. It is difficult to say for how long these precautions should be maintained. Recurrent disease more than 6 months after the initial diagnosis is rare, though possible. There have not been many reports of patients losing vision at these later stages of treatment. Any recurrence of ischemic neuropathy would be difficult to differentiate from the nonarteritic form. There is always a difficult balance to be achieved between the reduction of risk to vision versus the potentially dangerous side effects of the chronic use of corticosteroids. After 1 year, and at the latest 2 years, serious consideration should be given to a cessation of therapy. Some patients develop chronic myalgias at doses lower that 10 mg of prednisone. If it is felt that the disorder has evolved into a form of polymyalgia rheumatica, therapy may be required indefinitely for the relief of pain. In patients with chronic and unremitting arteritis (which is unusual) the use of nonsteroidal immunosuppressants (e.g., methotrexate or cyclosporine) can be of benefit. This sort of steroid sparing strategy requires the participation of an internist/rheumatologist for proper case management.

Compressive Optic Neuropathy

: Definition

Compressive optic neuropathy is the impairment of optic nerve function by space-occupying lesions that mechanically compress the optic nerve or optic tract. With only a few exceptions, these disorders are largely

benign neoplasms or arterial aneurysms, which are discussed in detail in Chap. 12. A brief review of the fundamental principles is discussed here.

Signs and Symptoms of Compressive Optic Neuropathy

The optic disc in an eye with a compressive neuropathy can be normal, swollen, or atrophic. The appearance depends on the timing, location, and duration of the compression. Atrophy of the disc (signs of pallor and loss of nerve fiber bundle striations) indicates that there has already been some permanent damage to the optic nerve, and a full recovery of function will not be possible. A swollen optic disc indicates that the site of compression is in or near the orbital apex. Orbital masses (including the swollen rectus muscles of Graves' disease) are usually marked by the presence of local orbital signs, such as proptosis, chemosis, somatosensory loss, and/or mechanical strabismus. Chiasmal region compression is marked by hemianopic visual field defects that respect the vertical meridian, often including contralateral, "asymptomatic" eyes, and frequently affecting the central 30° (of eccentricity) of the visual field. Intracanalicular compression of the nerve (within the optic canal) can produce visual field defects that are uncharacteristic, variable in shape, and slowly progressive. Occasionally, lesions like meningiomas arising in this region are mistakenly diagnosed as glaucomatous optic neuropathies. The visual acuity and field of an eye suffering compressive damage to the optic nerve can remain largely unaffected, or only marginally impaired, for long periods. An RAPD in such cases is the hallmark that should alert the examiner to the presence of an optic neuropathy.

! Note

Every chronic, progressive visual impairment should raise the suspicion of a compressive mass, unless definitive proof of an alternate mechanism is found.

Occasionally, several attempts at definitive diagnosis are needed prior to successful detection of an intracanalicular tumor. The diagnostic modality of choice is the MRI. Such imaging is strongly indicated in cases of visual field loss that respect the vertical meridian. One must also include the possibility of a so-called pituitary apoplexy, in which a hemorrhagic infarct in a rapidly growing tumor results in a rapid expansion in its size with marked loss of vision in one or both eyes. This life-threatening situation can easily be confused with a demyelinating optic neuropathy.

Treatment of Compressive Optic Neuropathies

Treatment of compressive lesions is mostly surgical. Inoperable or poorly operable meningiomas can sometimes be successfully managed with external radiation. Medical therapy is effective in the treatment of prolactin-secreting pituitary adenomas, using dopamine agonists such as bromocryptine (see Chap. 12). Such tumors carry a high risk of rapid growth during pregnancy. Therefore, such cases require frequent perimetric study. Life-long ophthalmic follow up is important for managing this group of disorders.

Optic nerve and chiasmal gliomas in children require especially attentive care. Regardless of whether neurofibromatosis is present or not, a very cautious approach to management is needed. Radiation therapy is indicated when the tumor shows a tendency toward rapid growth, which, however, is not the usual case. In children under 8 years of age, irradiation is to be avoided, given the high probability late complications. For small children, a chemotherapeutic approach to slowing the tumor growth is preferable. In many cases these tumors can behave as if they are dormant, showing no signs of growth for many years. A surgical approach to managing exophytic tumors is logical in those cases showing signs of tumor expansion. Given the small number of cases involved, pediatric patients should be managed at tertiary referral centers.

Uncommon Optic Neuropathies

Radiation Optic Neuropathy

: Definition

Radiation optic neuropathy is a consequence of high-dose radiation therapy delivered to the region of optic nerve and/or chiasm, which often presents abruptly in a manner that mimics acute retrobulbar optic neuritis. The loss of vision is usually profound and there is no effective therapy to reverse the process, once it has begun.

An interval of 9 to 12 months (or more) after radiation therapy is the usual temporal sequence, and the optic disc is initially normal in appearance (hence the similarity to the presentation of demyelinating optic neuritis). The pathogenesis is thought to be ischemic, caused by loss of capillary endothelial cells that cease growing and die out, leading to expanding areas of capillary dropout and radiation necrosis within the nerve. High-dose corticosteroid therapy and hyperbaric oxygen therapy have been tried, but with no success. The prognosis is usually grim (see Chap. 23).

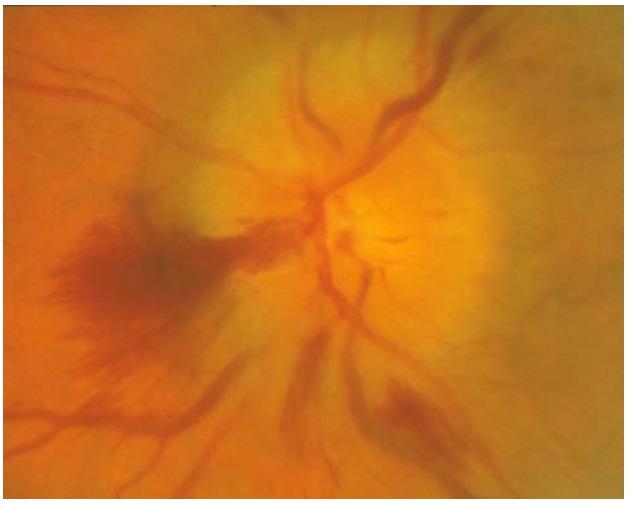

Fig. 8.21. Optic disc appearance in a patient with an infiltrating optic neuropathy and chronic myeloic leukemia

Infiltrating (Carcinomatous) Optic Neuropathies

Definition

A **carcinomatous optic neuropathy** is a visual loss with an optic neuritis-like onset, caused by carcinomatous, lymphomatous, leukemic, or inflammatory disease (e.g., sarcoidosis) with an initially normal appearing optic disc or with disc edema.

Corticosteroid therapy usually yields a quick, though temporary, improvement in vision. This rapid response is often a clue to the underlying pathogenesis, which is often a recurrence of a previously diagnosed neoplastic or orbital inflammatory disease (■ Fig. 8.21).

In all such cases, a therapeutic trial of steroid therapy (1 mg/kg body weight) is indicated. This type of treatment would be contraindicated for typical cases of demyelinating neuritis, meaning that a clinical distinction between secondary infiltrating and primary demyelinating processes must be made early on. When a bacterial infection such as orbital cellulitis is recognized, antibiotic therapy must be given priority over any consideration of immunomodulating drugs.

Toxic Optic Neuropathies

Definition

A **toxic optic neuropathy** is a bilateral optic neuropathy caused by the neurotoxic effects of medications (usually chronic) or environmental toxins (acute or chronic).

Ethambutol and other antitubercular drugs, cytostatic agents, heavy metals, hexachlorophene, and methanol can all cause a toxic optic neuropathy (also see Chap. 17). The first priority is to identify the offending agent and then to block further exposure. Specific measures that follow are determined by the nature of the toxin. The most common syndrome of toxic damage to the optic nerve/chiasm is that of tobacco–alcohol amblyopia. It is thought that the toxin in question is cyanide, which is present in trace quantities in tobacco smoke. Interventional therapy with oral multivitamins (e.g., vitamin B complex) and intramuscular injections of hydroxycobalamine (the decyanated form of vitamin B_{12}) can reverse the visual loss in the early stages of the disease. These vitamins are thought to chelate trace levels of cyanide and detoxify the affected tissues. Some individuals may be more at risk than others are, based on the composition of their mitochondrial DNA and variations in the cytochrome oxidase enzymes expressed in their mitochondria. If the optic disc is not visibly atrophic at the time of the diagnosis, there is a good prognosis for visual recovery. Atrophic optic discs mean that any treatment is probably futile. In the case of suspected methanol intoxication, MRI scanning of the brain will often show degeneration in the basal ganglia.

Note

An early symptom of toxic optic neuropathy is that of color vision impairment. Hue discrimination tests like the Farnsworth panel D-15 or the Farnsworth-Munsell 100 hue can be useful when monitoring antitubercular therapy. Ideally, a baseline record of color vision performance should precede the start of treatment.

Optic Neuropathies of Malnutrition

Definition

An **optic neuropathy of malnutrition** is one caused by a dietary deficiency. In the developed parts of the world, this is most commonly a deficiency of vitamin B_{12}. Such cases are uncommon, and are most often caused by macrocytic anemia. Vitamin B_{12} and folate levels are easily measured. Other risk factors for malnutrition include intestinal bypass or gastric stapling for weight loss and the hepatic cirrhosis of alcoholism. Treatment should include intramuscular injections of high doses of hydroxycobolamine.

Note

Cyanocobolamine should not be used, as it has much less effect for chelating trace cyanide than hydroxycobolamine does.

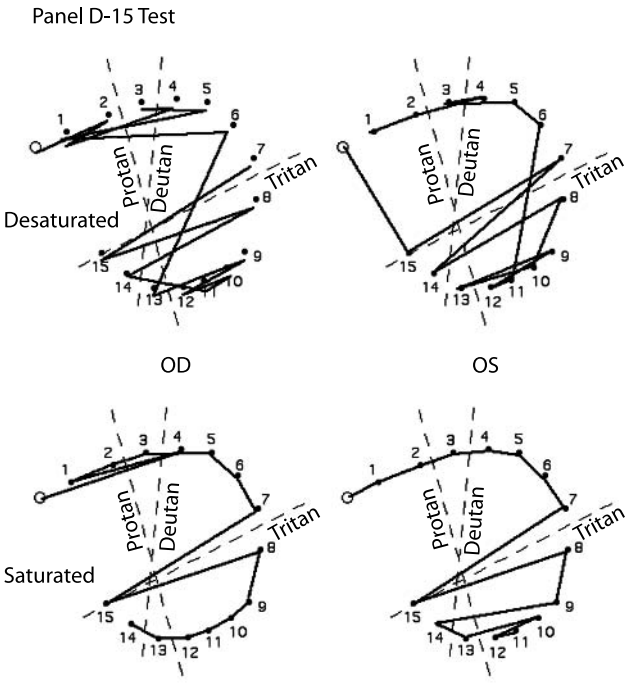

Fig. 8.22. Panel D-15 test of hue discrimination in a patient with autosomal dominant optic atrophy (ADOA). In typical cases one often finds strong impairment of blue perception

Autosomal Dominant Optic Neuropathies

Definition

An **autosomal dominant optic neuropathy** is a heredofamilial optic neuropathy associated with a mutation on chromosome 3, manifested as bilateral optic atrophy in children and young adults.

Autosomal dominant optic neuropathy (ADOA) affects both sexes equally. The functional impairment of vision and the penetrance of the dominantly inherited trait are highly variable. A few patients will have Snellen acuities as poor as 20/200, and a few will have normal acuity. The visual field suffers limited damage in the form of relative cecocentral depressions. The pattern seen on static testing of the central visual field can mimic the appearance of a (pseudo)bitemporal visual field defect, which sometimes leads to a misdiagnosis of a chiasmal syndrome. In mild, early cases, the visual field can have an almost normal appearance. Reading ability is usually good. There is a limited course of progression with age. Typically, a blue/yellow hue discrimination deficit is present. Red/green deficiencies are less common. The Farnsworth panel D-15 and ophthalmological testing of the relatives of the patient will lead to a quick confirmation of the diagnosis (■ Fig. 8.22). Many affected individuals are unaware that their visual function is subnormal. There is no effective therapy.

Leber's Hereditary Optic Neuropathy

Definition

Leber's hereditary optic neuropathy (LHON) is a mitochondrially inherited, severe, initially monocular but within weeks binocular visual loss, most commonly in young men.

The visual acuity in LHON is reduced to 20/200 or worse. The visual field shows a large, central or cecocentral scotoma, and color perception is badly damaged. The acute phase is marked by a peripapillary microangiopathy with irregular areas of microvascular dilation, tortuosity, and variations in caliber sometimes described as telangiectasias. The next stage (within a few weeks) is marked by increasing optic disc pallor and a disappearance of the initial microangiopathy. It is notable that the microangiopathy can be found in asymptomatic carriers of the maternally inherited deficit.

The diagnosis can be confirmed by identification of the causative mutations in the mitochondrial DNA (point mutations, usually at nucleotide positions of 3460, 11778, or 14484, and much less commonly, other sites). There is no specific or effective therapy. Patients and their families should be told to avoid sources of trace cyanide (secondary exposure to cigarette smoke and cyanide-carrying foods such as bitter almonds, apricot pits, pear or apple seeds, and white lima beans).

Pearl

Many previously idiopathic cases of optic atrophy have been correctly identified as LHON through molecular genetic testing. In cases where the cause remains in doubt, the use of such tests is often helpful (see Chap. 18).

Other Hereditary Optic Neuropathies

Other heredofamilial optic neuropathies are very uncommon. They are encountered primarily in cases in which additional, and unexpected, deficits develop. Behr's recessive optic atrophy affects young males under 10 years of age, accompanied by mild cognitive impairment, spasticity, ataxia, and muscular hypertonicity. A rare form of recessively inherited optic neuropathy is found accompanied by type I diabetes, deafness, and diabetes insipidus (hence DIDMOAD: *d*iabetes *i*nsipidus, *d*iabetes *m*ellitus, *o*ptic *a*trophy, and *d*eafness – or Wolfram's syndrome). Optic atrophy also commonly develops in conjunction with various forms of spino- or olivocerebellar degenerations, such as Friedreich's ataxia.

Traumatic Optic Neuropathy

Definition

A **traumatic optic neuropathy** is one caused by trauma to the optic nerve, most frequently in the setting of a traffic accident with cranial and/or midface fractures.

Traumatic optic neuropathy results primarily from indirect injury, rather than by direct crushing or tearing mechanisms. A direct blow to the eye can cause an avulsion of the optic nerve (more properly called an expulsion). The mechanism appears to be one of a sudden, explosive increase in intraocular pressure with rupture of the scleral coat in a circumpapillary ring where the sclera is very thin. Most often, this occurs in patients that have moderate to high degrees of axial myopia and/or a posterior staphyloma. The eye has no light perception, the pupil is fixed in mid-dilation, and ophthalmoscopy reveals disappearance of the optic disc, with folds of retina that have been dragged through the posterior rupture. Another mechanism appears to be a small-vessel infarction of the intracanalicular portion of the nerve, presumably caused by shearing of the perineural blood vessels. This commonly happens without a fracture, and there is initially no ophthalmoscopic abnormality. The eye has no light perception, there is a normal disc appearance, and there is a profound RAPD. When seeing acutely injured patients, as in an emergency room setting, the single most important bit of objective data is the presence or absence of an RAPD. The disc will often be normal in appearance, only to develop manifest atrophy over the ensuing 6 weeks. Penetrating orbital injury with direct damage to the optic nerve is much less common. Treatment in this setting is controversial. Despite many attempts to study this problem, it is not known whether (1) surgical decompression of the orbit and/or optic canal, (2) removal of orbital bone fragments in contact with the nerve, or (3) conservative management with high doses of intravenously administered corticosteroids is the better method. Megadose corticosteroids are most commonly used, since the surgical approaches carry the additional risk of high morbidity with uncertain benefit.

Optic Atrophy after Papilledema

Definition

damage to the optic nerve caused by chronic papilledema.

If elevated intracranial pressure goes undetected, bilateral loss of vision can develop, because chronic papilledema often leads to gliosis and atrophy of the optic nerve. The same problem can develop if the cause of the elevated pressure cannot be corrected. The pathogenic mechanism is not well understood, but ischemia is thought to play an important role. The time needed to develop this complication is variable and is not predictable in individual cases. The transient obscurations of vision often associated with papilledema seem to be unrelated to the risk of atrophy. The visual impairment can begin acutely or subacutely, often with arcuate visual field defects that are very similar to those in patients with chronic open-angle glaucoma, and as is the case with glaucoma, the central-most portions of the visual field are initially spared. The process, once begun, can seem impossible to stop, resulting in total optic atrophy and blindness. Patients with chronic papilledema need to be monitored by an experienced ophthalmologist. Papilledema that threatens in this manner (i.e., moderate to marked levels of papilledema that last longer than a few weeks) must be brought under control, either by shunting procedures or high-dose acetazolamide therapy. Serial lumbar punctures are not usually a satisfactory method of control. While a lumbar puncture is essential to establish the initial diagnosis, it rarely needs to be repeated. Patients under this type of threat to their vision can also benefit from optic nerve sheath fenestration. This type of procedure is not effective for control of headache, but can reverse the disc swelling and protect the optic nerve.

Optic Atrophy after Damage to the Optic Tract

Definition

Optic atrophy after damage to the optic tract is a characteristically bilateral, though asymmetric, form of optic atrophy that develops in patients with chronic lesions of the optic tract.

Lesions affecting this last portion of the third neuron (see Chap. 3) produce a characteristic pattern of optic atrophy that is ophthalmoscopically manifest within several weeks or months after the damage (also see Chap. 19). Corresponding to the course of the nerve fibers, the atrophy in the disc ipsilateral to the damaged tract is vertically oriented, causing pallor in the superior and inferior quadrants of the optic disc. The contralateral eye, which suffers loss in the temporal half of the visual field, develops the opposite pattern of atrophy, preserving the superior and inferior quadrants, but causing a horizontal band of pallor extending across the disc. Its shape has been likened to that of a bow tie. The asymmetry of the atrophy is most evident in the nasal quadrants: The eye ipsilateral to the lesion has preserved color in the nasal quadrant, while the disc of the partner eye has a pale color in the nasal quadrant (see ■ Fig. 8.23).

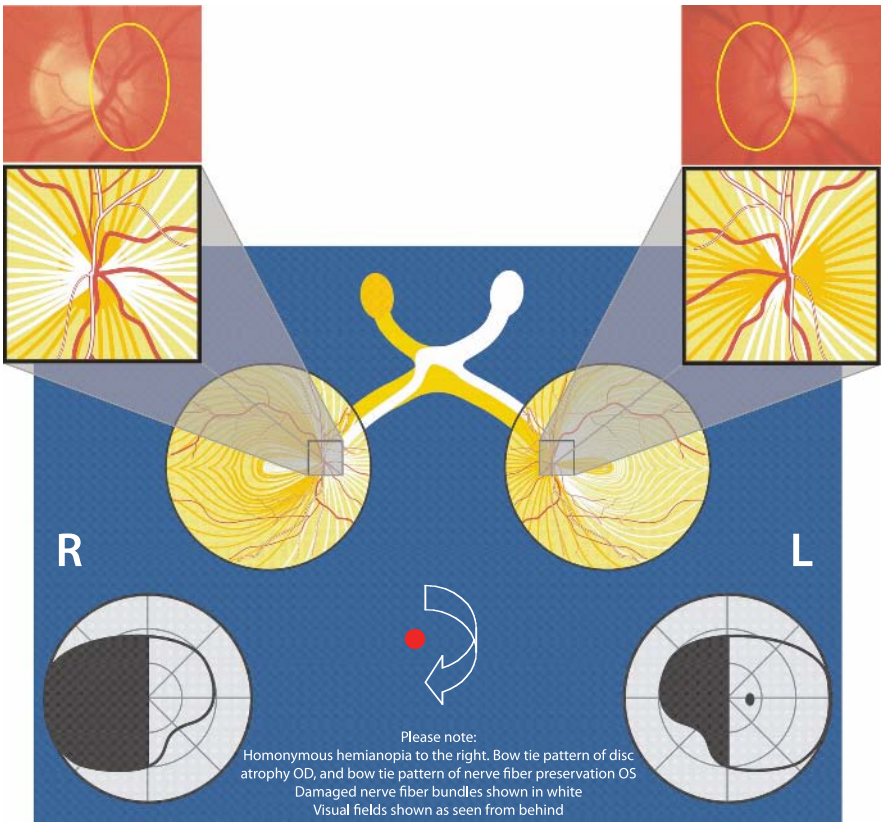

Fig. 8.23. The characteristic appearance of bilateral, asymmetric partial optic atrophy associated with a lesion of the left optic tract, causing a homonymous hemianopia to the right (n.b.: The drawing of the visual field defects in the *lower third* of the picture is drawn from the examiner's perspective, as if seeing the patient's visual field charts transparently from behind). The drawings of the neuronal pathways (*across the middle third* of the picture) portray the damaged axonal fibers as *white lines*. In the *boxed insets* are magnified diagrams of the optic discs' appearance. Note the asymmetry of the disc atrophy, which is particularly evident when comparing the nasal quadrants of the discs. The atrophy in the nasal quadrant of the eye contralateral to the lesion is markedly atrophic, while the nasal quadrant in the ipsilateral eye retains a healthy color. (Compare the zones marked by *yellow ovals* in the disc photos at the *top* of the figure)

Conclusion

Optic neuropathies play an important role among neuro-ophthalmic disorders. The physician faces a significant challenge when trying to differentiate ischemic, toxic, and degenerative disorders from compressive diseases of the optic nerve. ■ Table 8.2 p. 114 reviews some of the clinical elements that provide clues to the correct diagnosis.

Further Reading

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Chapter 9

Neuro-Ophthalmic Aspects of Orbital Disease

S. Pitz

Orbital diseases are distinct from primary ocular disorders in that they require consideration of a much larger group of differential diagnoses. Thus, ptosis may be attributable to a "simple" problem in the anterior segment, but may also be the clinical presentation of a more general disorder, such as Horner's syndrome, oculomotor paralysis, or myasthenia gravis. One must also consider orbital involvement in primary disorders of the periorbital structures, including the paranasal sinuses and the intracranial space.

Basic Orbital Anatomy

Structures surrounding the orbit and the proportional distribution of structures within the orbit are schematically diagrammed in ■ Fig. 9.1. The close relationship of the orbital walls with the paranasal sinuses is particularly important (■ Fig. 9.2).

In company with the optic nerve, the optic canal also conducts the ophthalmic artery and the postganglionic sympathetic fibers that arise from the carotid plexus. All three of these structures feed through the annulus of Zinn, a surrounding ring of connective tissue that anchors the origin of all four rectus muscles (■ Fig. 9.3).

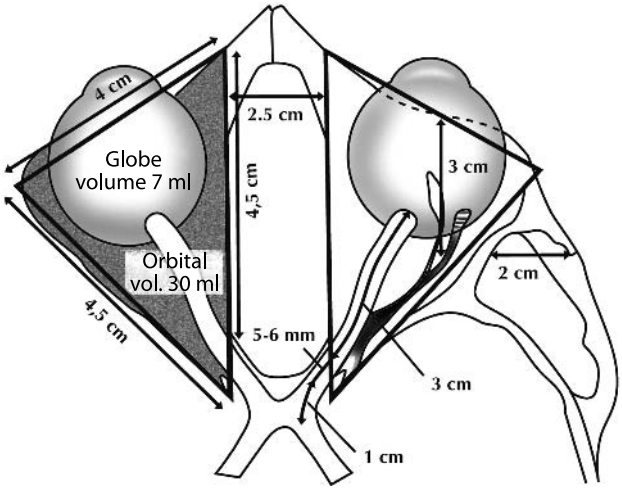

Fig. 9.1. Spatial relationships and comparative sizes of orbit, optic nerve, and chiasm (modified after Rootman; see Further Reading)

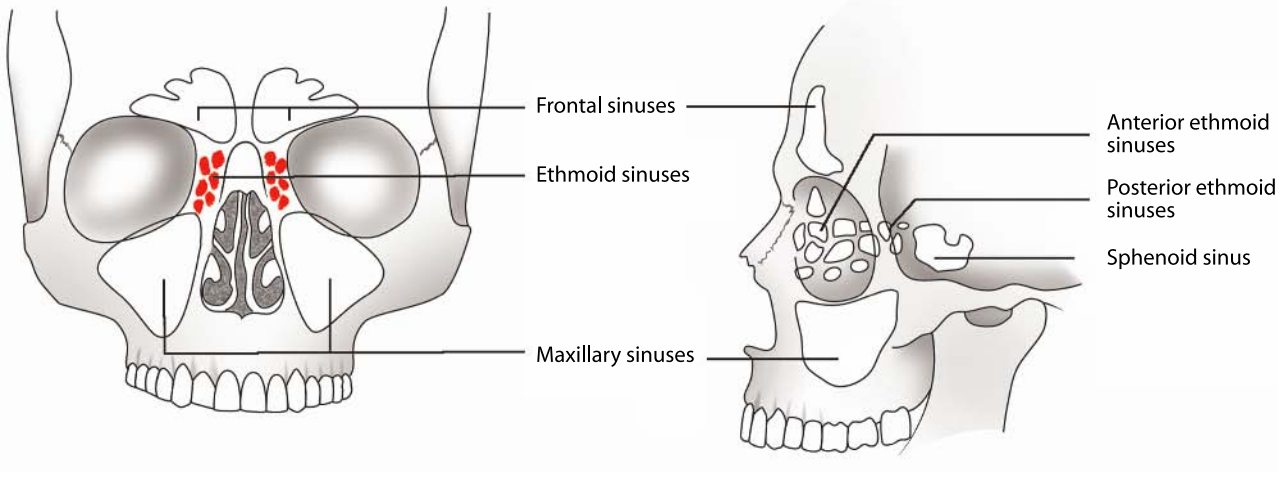

Fig. 9.2. Regional relationships between the paranasal sinuses and the orbits

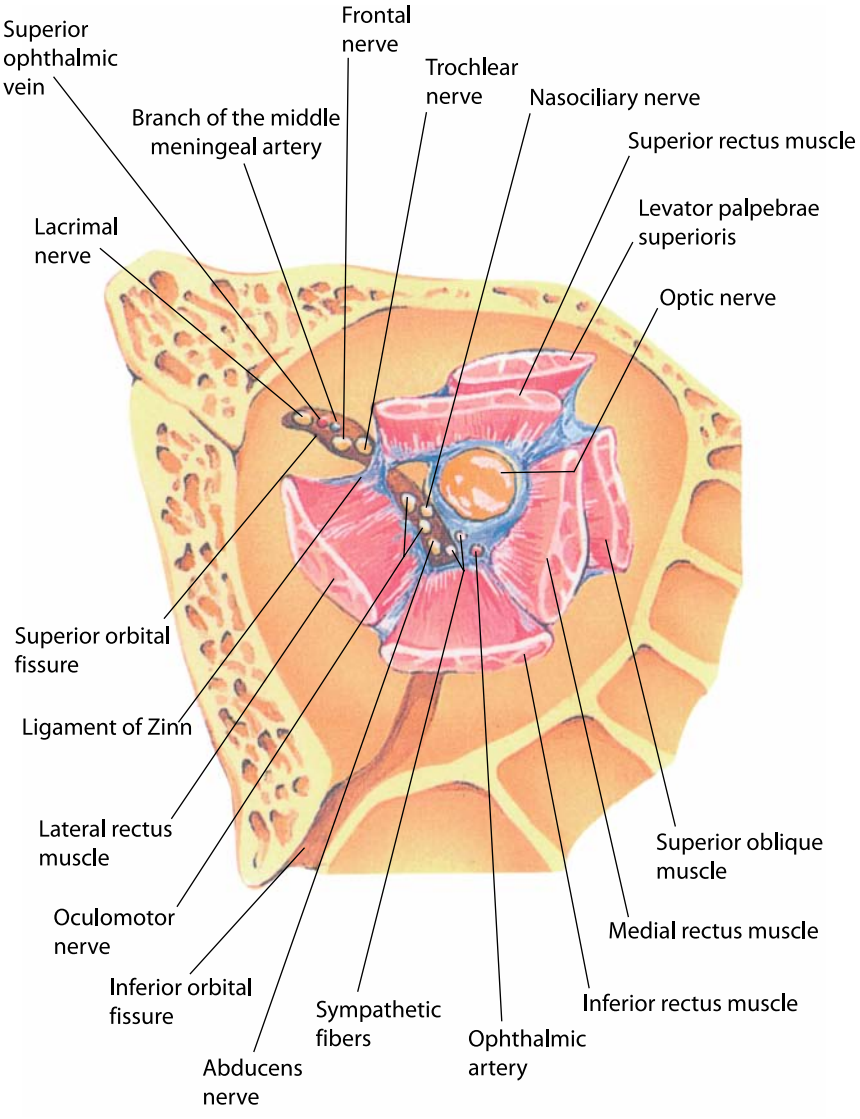

Fig. 9.3. Coronal plane section of the right orbital apex as seen from within the orbit and the various structures that pass through the optic canal, the superior orbital fissure, and the inferior orbital fissure. The optic nerve is at the center, emerging from the canal to pass through the annulus of Zinn. Superolateral to the canal lies the superior orbital fissure. Structures passing through the fissure (ordered from cranial to caudal) include the lacrimal nerve, the superior ophthalmic vein, a branch of the middle meningeal artery, the frontal nerve, and the trochlear nerve. Farther below, the oculomotor nerve, the nasociliary nerve, and sympathetic nerve fibers pass through the tendinous annulus of Zinn. The ophthalmic artery also passes through the canal and the annulus, along a course located inferior to the optic nerve (modified from Stewart; see Further Reading)

Pearl

Given the restricted space within the optic canal and the fibrous connections between the dura, the periosteum of the orbital walls, the dural sheath of the nerve, and the annulus of Zinn, inflammation in this region causes pain when the rectus muscles contract. Pain on eye motion is a common feature of demyelinating optic neuritis (see Chap. 8), and the afferent somatosensory pathway is by way of the nasociliary nerve.

Another important structural feature of the orbit is the superior orbital fissure, which provides access to the orbit for nearly all other vascular and neural structures that support ocular function. It is formed as an opening between the greater and lesser wings of the sphenoid. The important structures passing through the fissure are illustrated in ■ Fig. 9.3. The superior ophthalmic vein is the most functionally important venous exit from the orbit. It flows into the cavernous sinus. The nasolacrimal nerve, arising from the ophthalmic division of the fifth cranial nerve, supplies the lacrimal gland and the frontal nerve divides into two primary branches, the supratrochlear nerve and supraorbital nerve. These two provide the afferent sensory pathway for the forehead and upper lid.

While the oculomotor and the abducens nerves both pass through the tendinous annulus at the orbital apex to innervate the extraocular muscles from within the intraconal space, this is not the case for the trochlear nerve. Its relatively "unprotected" intraorbital course (external to the muscle cone and close to the orbital roof) contributes to its greater vulnerability in cranial injuries. The trochlear is also the thinnest and longest of the cranial nerves, arising from the dorsal midbrain and decussating through the anterior medullary velum. The thin tissue through which the trochlear nerves pass is easily damaged in closed-head in-

juries due to torsional stresses that lead to tearing and bleeding. This is a common cause of bilateral fourth nerve palsies.

The inferior orbital fissure is connected to the superior orbital fissure. Through its cleft is a communication between the orbital contents and those of the pterygoid fossa. It contains the inferior ophthalmic vein, which drains blood from the inferior orbital structures, including the inferior portions of the globe (via the inferior vortex veins). It then empties into the pterygoid plexus. This soft tissue passage between the orbit and the pterygopalatine fossa provides a pathway of least resistance for the spread of pathologic processes, including bacterial infections and malignant cancers. The volume of venous flow through the inferior fissure is smaller, more variable, and less important than the flow through the superior ophthalmic vein. This passage also contains the infraorbital nerve, which arises from the maxillary division of the trigeminal nerve and passes through the foramen rotundum in the skull base and then through the inferior orbital fissure. It courses along the orbital floor in a groove on the dorsal surface of the maxillary roof, partly covered by connective tissue, and then through the infraorbital canal to innervate the lower lid and portions of the upper cheek.

Pearl

Fractures of the orbital floor, in addition to causing mechanical and paralytic disturbances of ocular motility, also cause hypesthesia or complete somatosensory loss in the ipsilateral incisors, gingiva, cheek, and the mucosal surface of the upper lip.

The orbital connective tissues are thin and delicate, and they are difficult to demonstrate during surgical procedures. Nonetheless, they provide significant barriers to the spread of diseases between the various compartments that they form: Tenon's capsule is a barrier that extends from the limbus to the dural sheath of the optic nerve, separating the globe from the remainder of the orbital contents. Connections between Tenon's capsule and the sheaths of the extraocular muscles form a conical space in the retrobulbar orbit that is separated from the remaining structures that lie outside of the cone.

Pearl

In the setting of orbital floor fractures, the typical mechanical restriction of elevation and depression is more often the result of entrapment of the connective tissues surrounding the inferior rectus, rather than a direct hold on the muscle itself.

Signs and Symptoms of Orbital Disease

Exophthalmos

The confined space within the bony orbit limits the expansion of orbital contents, which then prolapse through its anterior opening. This is the signal feature of many orbital diseases. Pulsating exophthalmos is a common accompaniment of structural defects in the sphenoid wings (Neurofibromatosis) or with vascular disorders like arteriovenous fistulas. The pulse synchronous movement of the globe is most easily seen during applanation tonometry, when the applanated circle surrounded by the tear film meniscus can be seen pulsing.

Note

Pseudoexophthalmos is a term to describe an apparent forward protrusion of the globe caused by primary ocular disorders, such as high axial myopia, rather than by pressure on the globe from enlarged retrobulbar structures.

Diplopia

Binocular diplopia can arise by three different mechanisms: by displacement of the globe, by damage to of the motor cranial nerves, or by damage to the extraocular muscles (e.g., Graves' disease, chronic progressive external ophthalmoplegia, or myasthenia).

Changes of Lid Position

Ptosis

■ Table 9.1 provides an overview of the potential causes of ptosis.

Video 9.1

Table 9.1. The causes of ptosis

Congenital ptosis (■ Fig. 9.4)	Can be isolated, associated with an ipsilateral elevator palsy, or with the familial fibrosis syndrome, or with mandibulopalpebral synkinesis (The Marcus-Gunn jaw-winking phenomenon)
Acquired ptosis	Involutional (age-related dehiscence of the levator tendon), innervational (third nerve palsy, Horner's syndrome), myasthenic, or with chronic progressive external ophthalmoplegia, chronic use of contact lenses, or topical preparations of corticosteroids

Table 9.2. The causes of lid retraction

Disease	Pathogenesis
Graves' disease	Initially driven by sympathetic hypertonus in Müller's muscle, later by the inflammatory fibrosis of chronic myositis
Dorsal midbrain disease (so-called Collier's sign)	Loss of inhibitory supranuclear input to the third nerve nuclear complex
Intracranial hypertension	Mechanism thought to be similar to the effects of dorsal midbrain disease
Topical glaucoma drugs (epinephrine, Dipivefrin, clonidine/apraclonidine)	Sympathomimetic effect
Mechanical retraction of the upper lid	Surgical effect, mass effect

Lid Retraction

■ Table 9.2 lists the disorders that commonly cause lid retraction.

Pseudo–lid retraction must be ruled out (unilateral because of compensation for a contralateral ptosis, or bilateral lid retraction caused by hypersympathotonia, such as in thyroid storm, anxiety, or panic attacks).

Pearl

Lifting the ptotic lid will allow normalization of the retracted upper lid position contralateral to a monocular ptosis.

Loss of Vision

Orbital diseases cause impairment of vision, whether mild or severe, by one of two primary mechanisms. On one hand, the globe may be distorted or displaced by direct contact with a space-occupying process, and on the other hand, the optic nerve may be damaged by direct compression.

Chemosis

Chemosis is associated with a variety of usually benign disease processes in the anterior segment, but can also be typical of a group of orbital disorders: orbital inflammatory diseases, such as idiopathic inflammatory pseudotumor, ocular myositis, dysthyroid ophthalmopathy, or any impairment of venous outflow from the orbit (e.g., carotid–cavernous fistula or infiltrating orbital malignancies).

Diagnostic Methods

■ Table 9.3 summarizes the various diagnostic methods used for the study of orbital disease.

A rational plan for treatment also requires additional testing in the form of MRI and/or CT imaging. Ultrasonography is most suited to the study of midorbital structures. Study of anterior orbital structures requires the use of a standoff method, such as immersion of the probe in a water bath that covers the eye. The posterior third of the orbit cannot be imaged by ultrasonography, due to both limited tissue penetration by the sound and by reverberations of the sound off of the closely approximated surfaces of the bony orbital walls. Duplex echography is particularly helpful when studying space-occupying lesions that arise from vascular disorders, such as hemangiomas, arteriovenous communications, and dural sinus fistulas. It can determine the direction and relative volume of blood flow in the orbital vessels, which is a particularly helpful and noninvasive method. The physician planning the study and treatment of orbital diseases must rely primarily on tissue biopsies, and MRI and CT imaging of orbital hard and soft tissues. The choice between MRI and CT is governed by the nature of the disease (disorders of soft versus those of bone tissues, for example). Additional important considerations include the time needed for the studies. CT scanning is quicker and less affected by movement artifacts, and is thus advantageous for cases of children or elderly patients with a limited capacity to lie quietly still.

Note

Patients with cardiac pacemakers cannot be safely scanned by MRI, since the strong magnetic field can cause the device to malfunction or its battery to overheat or change its position, all of which are potentially fatal consequences.

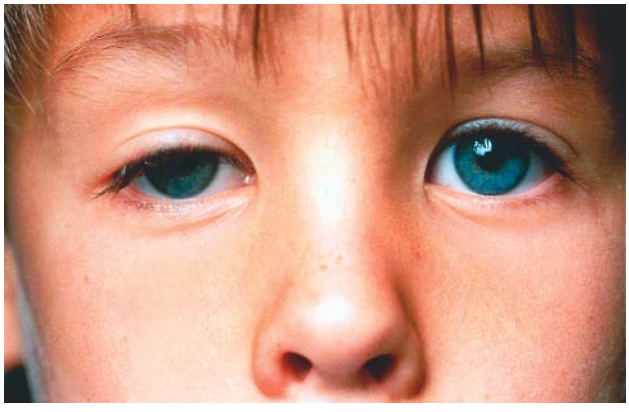

Fig. 9.4. A small boy with congenital ptosis. Most striking is the asymmetry of the lid folds. On the ptotic side it is hard to identify and less prominently formed than its left hand partner. The optical axis of the eye is unobstructed

Table 9.3. Diagnostic testing for a suspected orbital mass

Signs and symptoms	Methods	Remarks
"My glasses no longer work"	Manifest refraction	Lenticular myopia of uncontrolled diabetes? Axial hyperopia due to proptosis by orbital mass?
Axial proptosis	Hertel exophthalmometry	Mismatch between eyes of up to 2 mm is within normal limits – there is high statistical variance between examiners and examinations. Always compare to base line measures.
Axial proptosis	View eye position of patient from above and behind, looking down over the patient's brow	Interocular differences >2 mm can be easily seen. Helpful when Hertel values show large interocular mismatch.
Horizontal or vertical globe displacement	Ruler Kestenbaum glasses	Compare with old photos of patient
Globe displacement	Palpation	Symmetrical resistance to retropulsion? Is there a bruit? Pulsatile exophthalmos? Crepitation?
Bruit	Auscultation	Murmur
Pupillary motility	See Chap. 5	
Ocular motility	See Chaps. 10 and 11	Forced duction tests when indicated
Interpalpebral fissure	10–12 mm	Measure at primary position when patient is fully relaxed; For monocular ptosis or lid retraction, measure eyes individually
	Compare upper lid positions in downgaze	Watch out for pseudowidening of lid fissure when contralateral to a ptotic lid; Vertical mismatch in downgaze (Graves' congenital ptosis – postsurgical shortening of upper lid)
Levator function	12–18 mm	Maximum lid excursion (from full downgaze to full upgaze positions) while restraining frontalis movements (Fix the forehead position in place with your hand placed horizontally across the brow)
Intraocular pressure	Applanation tonometry	Interocular mismatch? Gaze direction effect on interocular pressure (IOP): Measure IOP in primary and upgaze positions. When elevation is markedly limited, measure IOP in partial downgaze versus partial upgaze attempt.
Prominent episceral vessels	Slit-lamp examination	Vascular distention by obstruction to orbital venous outflow?
Fundus	Ophthalmoscopy	Retinal/choroidal obstruction to venous outflow Optic disc edema, choroidal folds

The CT scan is ideally suited to the study of bony structures, while the MRI is best suited to the diagnostic examination of soft tissues. To obtain optimal images in the coronal planes of the orbit the patient must lie in the prone position with the neck maximally extended. Coronal reconstructions of data obtained in transaxial views are significantly less detailed. For MRI scanning a recumbent position is used, which is better tolerated by the elderly and patients with poor joint flexibility. Lastly, the CT scan is the radiologic procedure that exposes the eyes' lenses to the greatest dose of radiation, while the MRI requires no exposure to ionizing radiation (also see Chap. 20).

Exophthalmos as the Presenting Sign

Graves' Disease

Clinical Features of Graves' Disease

Graves' disease (also called thyroid ophthalmopathy, dysthyroid ophthalmopathy, or endocrine orbitopathy) is an autoimmune disease that commonly, though not always, is associated with hyperthyroidism. It is accompanied by a broad spectrum of signs and symptoms of orbital inflammation. Chief among these is exophthalmos. Graves' disease is the most common cause of exophthalmos among

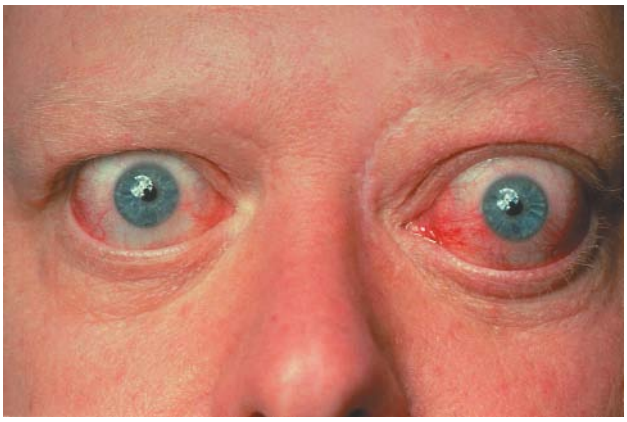

Fig. 9.5. A patient with Graves' disease. Striking proptosis, left more than right, with bilateral retraction of both upper and lower eyelids, and severe conjunctival hyperemia

adults, and it is usually a bilateral and often very asymmetric disorder. This can lead to misdiagnoses during the early stages of the disease.

Initial symptoms most commonly include foreign-body sensation, a feeling of retrobulbar pressure or pain, tearing, blurring, and photophobia. With later inflammatory involvement of the extraocular muscles, diplopia begins to appear. All of these symptoms have a diurnal cycle, with the most symptomatic period at the time of awakening in the morning. In addition, and virtually pathognomonic, is the appearance of lid signs, including lid swelling, lower lid retraction, upper lid retraction with lid lag (not moving in close synchrony with the globe during downward pursuit movements), and infrequent blinking or a staring expression (■ Fig. 9.5). These facial features are for many patients the most intolerable aspect of the disease. In addition, it can be accompanied by an acute or chronic swelling of the lacrimal gland. Other signs include conjunctival hyperemia, chemosis, plical hyperemia, injection over the rectus muscle insertions, and exposure keratopathy. Mechanical strabismus arises from inflammation in the medial and inferior rectus muscles, which are the two muscles most commonly affected. Fibrotic foreshortening of the muscles tethers the globe, limiting the ability to elevate or abduct the eye. Finally, a secondary glaucoma can develop and retinal or choroidal signs of optic nerve compression can appear. These include relative or absolute central scotomas, relative afferent pupillary defect, profound loss of visual acuity and color perception, and optic disc edema with surface exudates may be present. This is an emergent disorder that requires immediate reversal, usually accomplished by administering high doses of corticosteroids, followed by surgical decompression of the optic canal and orbital apex from an ethmoid approach.

Pathogenesis of Graves' Disease

Graves' disease is an autoimmune disorder. In 85% of cases there is initially a simultaneous autoimmune hyperthyroid state; in 10% of cases, a hypothyroid state; most of the due to Hashimoto's thyroiditis. In the remaining 5% of cases, the early stages of Graves' disease develop in the absence of any detectable thyroid dysfunction.

Diagnosis of Graves' Disease

The diagnosis of Graves' disease, aside from a history of thyroid problems, uses measures of visual acuity, pupillary light responses, and ocular motility. The configuration and movement of the lid margins should be carefully studied. The slit-lamp examination should include the measure of intraocular pressure by applanation tonometry both in downgaze and in the primary position. Because of the foreshortened rectus muscle's traction on the globe, attempts to force the eye into the primary position often result in a marked, though transient, elevation of the intraocular pressure. Visual field testing and a sonographic determination of rectus muscle thickness by A-scan complete the workup. Echographic confirmation of rectus muscle thickening in the midportions of muscle belly, but with no thickening at the tendinous insertions, is characteristic of Graves' disease and differentiates it from orbital myositis, in which the inflammatory swelling extends all the way to the point of insertion. In cases that remain in doubt as to the correct diagnosis, a thin-section CT scan of the orbit helps to rule out a mass lesion other than one or more swollen muscles. High-resolution MRI scanning with determination of the T2-relaxation time produces images that can be used to judge the water content in the rectus muscles, a correlate for inflammatory edema.

Treatment of Graves' Disease

When managing the problems of active Graves' disease, the following measures are known to be of benefit: maintenance of a euthyroid state, avoidance of cigarette smoking (very important), use of topical hydrating agents (with or without preservatives, as needed), and nonsteroidal anti-inflammatory drugs. These are largely supportive therapy, allowing time to pass and inflammatory activity to subside, while protecting vision in the meantime. This is adequate for a majority of cases. Infrequently, one encounters cases of fulminant inflammatory disease that threaten destruction of the eye through extreme exposure of the ocular surface and formation of corneal ulcers, or by compression of the optic nerve, which can destroy vision to the point of no light perception. The use of orbital irradiation and or surgical decompression should be saved for these very dangerous, high-risk cases. High doses of oral corticosteroids, such as 1 mg/kg of body weight of prednisone, can be used

for periods of about a month. Longer than a month's use, however, increases the risk of steroid use unacceptably. The drug is particularly valuable as a temporizing strategy for suppressing the inflammatory activity during the time leading to surgical decompression or radiation therapy of the orbital tissues. (For emergent intervention, 1,000 mg/day of intravenously administered prednisone given in doses of 250 mg every 6 h will occasionally allow rapid recovery of central vision). Radiation is given in ten equal, fractionated doses (usually on the weekdays of two consecutive weeks) to a total exposure of 12 to 20 Gy. A few reports conclude that there is benefit in combined therapy, in which the corticosteroid treatment is maintained all the way through the period of radiation treatment. There is no consensus of agreement on this issue, however. The radiation is meant to destroy the entire monoclonal population of lymphocytes that have targeted the orbital tissues. Benefits of reduced inflammatory activity can be expected within 6 weeks of completing the radiotherapy.

If optic nerve compression threatens permanent damage to vision, surgical decompression of the bony orbital walls can allow the excess volume of orbital tissues to herniate into the paranasal sinuses (medial and or inferior walls) or temporal fossa (lateral wall). Decompression increases the risk of strabismus, making management of the diplopia more difficult. Decompression is not very helpful for improving facial appearance, which is benefited far more by plastic surgical repositioning of the retracted eyelids, but this step has to wait for the last. Diplopia usually cannot be managed by prisms due to the nonconcomitant nature of the mechanical strabismus. Surgical recession of shortened rectus muscles should be deferred until there has been at least 6 months of stability in the angle of strabismus, but has a good prognosis for correction of the diplopia. Prism glasses are occasionally helpful at this last stage of recovery, and repair of the lid positions should be deferred until the strabismus surgery has been competed.

Pearl

Commonly, Graves' disease is accompanied by other autoimmune disorders, such as primary, chronic polyarthritis or ocular myasthenia, which can complicate the diagnosis and management considerably.

Tumors

Tumors of the orbit are usually heralded by symptoms arising from displacement of the globe's position in the orbit. Tumors within the muscle cone push the eye anteriorly, producing an axial proptosis and a shortening of the axial length (secondary hyperopia). Frequently, the patient's presenting complaint is contact of the eyelashes with the posterior surface of the spectacle lens. Extraconal masses usually displace the globe toward the orbital wall that lies opposite to the position of the tumor. The differential diagnosis can be refined based on the direction of displacement of the eye.

- Intraconal–axial proptosis
  - Hemangioma
  - Varix
  - Optic nerve sheath meningioma
  - Optic nerve glioma
  - Metastasis
- Extraconal superior orbital mass – inferodisplacement of the globe
  - Dermoid cyst
  - Lacrimal gland tumor
  - Mucocele
  - Lymphoma
- Extraconal inferior orbital mass – supradisplacement of the globe
  - Lymphoma
- Extraconal medial orbital mass – temporal displacement of the globe
  - Ethmoid or sphenoid sinus lesions (mucocele, carcinoma)
- Extraconal lateral orbital mass – medial displacement of the globe
  - Metastasis
  - Dermoid cyst

Idiopathic Orbital Inflammation

Clinical Presentation

Definition

Orbital inflammation presents as an acute onset, painful, monocular, space-occupying, orbital disease with clear signs of inflammatory activity. The ages of affected patients seem randomly scattered, including both small children and mature adults of all ages, including the very elderly. Classification of this heterogeneous group of disorders is based on the anatomical structures affected, and includes five subtypes (locations determined by MR imaging): a scleritic form, a dacryoadenitic form, a diffuse form, a myositic form (see below), and an apical form that also often involves the cavernous sinus (Tolosa-Hunt syndrome).

Ocular myositis affects primarily younger patients and is recognizable by its abrupt onset with a painful restriction of eye movement caused by a swollen rectus muscle. Curi-

ously, this is usually confined to just one muscle. Ocular myositis is often marked by visible hyperemia in the anterior segment of the eye, directly over and around the tendinous insertion of the affected muscle. Inflammatory orbital diseases are often accompanied by associated signs, such as lid swelling, ptosis, and/or exophthalmos. In a few cases, there may be an association with myasthenia gravis or a collagen vascular disease.

Pathogenesis of Idiopathic Orbital Inflammation

The genesis of this disorder is unknown. It is important to note that a number of systemic diseases can produce similar clinical findings. Thus, cases that have an unusual course or that show bilaterality (very uncommon for "orbital pseudotumor") should trigger the diagnostician's consideration of other disease categories.

Diagnosis

Frequently, the typically quick clinical response to systemic corticosteroid therapy helps to support the diagnosis. When the clinical presentation is ambiguous, a CT scan is essential. For cases with discrete findings limited to one area of the orbit, an MRI scan is preferred. When Tolosa-Hunt syndrome is suspected, an MRI is obligatory. The echographic signs in orbital myositis are pathognomonic. There is distention of the muscle belly, but also of the tissues at the tendinous insertion. This pattern of inflammation in an orbital muscle is never caused by Graves' disease.

The differential diagnosis includes lymphoma, sarcoidosis, tuberculosis, luetic disease, Wegener's granulomatosis, or several types of vasculitis. Wegener's granulomatosis is a generalized necrotizing vasculitis with ocular involvement in 40% of cases – most often in the form of axial proptosis (with associated scleritis or retinal vasculitis), but also as a form of myositis. Laboratory testing can help to establish the diagnosis of this autoimmune disease, if the c-ANCA (antineutrophile cytoplasmic antibody) shows cytoplasmic staining. The test is often negative in the early stages of the disease and should be repeated periodically, if the diagnosis is strongly suspected.

In uncertain cases or those in which a relapse occurs, a biopsy of the affected orbital tissues can be helpful. The histologic features are not pathognomonic and by themselves cannot establish the diagnosis. They can be highly varied in their appearance and are of value primarily when they can specifically identify such disorders as vasculitis or granulomatous diseases. Otherwise, the biopsy can help to relieve the uncertainty the process might be a secondary inflammation in the border region surrounding a neoplasm.

Treatment

Corticosteroids are the drugs of choice. Other immunosuppressants are not as effective. As a rule, when the diagnosis is first established, steroid therapy should start immediately (1 mg/kg of prednisone per day, slowly tapering the dose over an 8- to 12-week period).

! Note

A lymphoma would also respond initially to this treatment, for which reason a very careful monitoring of the patient's course is essential.

A repeatedly relapsing course of the disease, or a case in which corticosteroids are contraindicated, can be very difficult to manage. Most helpful in such cases is the use of orbital irradiation, or in some instances the use of surgical debulking can be considered. For Wegener's granulomatosis, treatment that combines the use of cyclophosphamide and corticosteroids will produce a remission in 90% of cases.

Orbital Cellulitis

Orbital cellulitis is characterized by the typical triad of exophthalmos, eyelid swelling, and limited ocular motility. The latter feature distinguishes orbital cellulitis from the more limited case of cellulitis of the lid, in which the eye's movements are unrestricted, and the prominence of the eye is confined to the tissues external to the orbital septum. This can be difficult to judge when the lid swelling is so pronounced that the eye cannot be seen. There is usually an associated fever, a leukocytosis, and history of repeated bouts of bacterial sinusitis. Such cases must be managed quickly and aggressively with hospitalization, intravenous antibiotics, and surgical incision and decompression of the swollen orbital tissues.

! Note

Orbital cellulitis carries a high risk of progression to a septic cavernous sinus thrombosis, since the veins and venous sinuses of the brain have no valves to limit the spread of sepsis.

In almost all cases, a CT scan of the paranasal sinuses will be needed. When there is no favorable response to antibiotic treatment, the possibility of trauma with an occult intraorbital foreign should be considered. In immunocompromised patients or those with diabetes mellitus, one should think of a possible mucormycosis, a condition with an extremely poor prognosis.

Orbital Varix

A varix is most often associated with a variable exophthalmos that changes with body position or with variations in intrathoracic pressure and has no audible bruit. This distinguishes a varix from a carotid–cavernous fistula. The problem most often manifests itself during the first or second year of life. The varix can be variably positioned deep within the orbit or in the subcutaneous tissues anterior to the orbital septum.

Occasionally acute and rapid increases in size (by thrombosis in or hemorrhage around the varix) mark the first presentation of the disorder. Despite this dramatic appearance, damage to vision by compression of the optic nerve is extremely uncommon.

The underlying genesis is thought to lie in a congenital venous malformation. A varix can be identified by using Valsalva maneuvers, ultrasonography, CT scanning, or MRI.

Usually no treatment is necessary. Only in cases of ocular or neural compression by acute hemorrhaging is it necessary to use surgical decompression. Identification and excision of the varix can be extremely difficult, and is not usually indicated.

Paranasal Sinus Disorders with Orbital Involvement

The clinical changes are determined in part by the site of the affected sinus and the disease process it contains (whether the disease is inflammatory or neoplastic infiltrating or space occupying). A benign form of space-occupying disease is the mucocele. A mucosal cyst is formed, initiated by obstruction of the affected sinus, that grows steadily larger, wearing through a bony defect in the sinus wall (pressure atrophy of bone by the steadily expanding mucoid cyst) until it begins to expand within the orbit, causing slowly increasing pressure on all of the orbital contents. There usually is a history of past sinus surgery, sometimes years ago. The most common malignancy to invade the orbit in this manner is squamous cell carcinoma.

The workup should include a consultation with an ear, nose, and throat surgeon, a CT scan and/or an MRI (thin sections with the highest available levels of image resolution). Treatment is determined by the nature of the underlying problem.

Cavernous Sinus Disease Affecting the Orbit

As a rule, lesions within the cavernous sinus produce complex disorders of ocular motility, simultaneously affecting more than one cranial nerve. The abducens nerve and the postganglionic fibers of the sympathetic pathway are more severely affected. In contradistinction to the cranial nerves that are protected within the lateral wall of the cavernous sinus (third, fourth, and fifth) the sixth nerve is suspended within the sinus, where it can be damaged most easily. An abducens palsy that is accompanied by an ipsilateral Horner's syndrome most commonly reflects the presence of an intracavernous disease process. A cavernous sinus meningioma arising in the lateral wall of the cavernous sinus usually presents as a chronic, slowly progressive loss of third nerve function with signs of aberrant regeneration. Additional signal symptoms of disease in this region include loss of somatic sensation in V_1 and V_2 (see Chap. 10). A carotid–cavernous fistula can be clinically dramatic, causing a pulsating proptosis with a strikingly red eye (high orbital venous pressure with "arterialization" of the episcleral veins).

see also Poster 10.1

Presentation with Enophthalmos

Orbital disorders that cause an enophthalmos are relatively uncommon, when compared with the frequency of exophthalmic disorders. They are collectively summarized here.

Clinically, they present as a monocular process in which the eye has receded into the orbit, as compared with the position of the contralateral eye. Depending on the extent of the posterior displacement of the globe, a deeper sulcus above the upper eyelid will be evident.

Measurements taken with the exophthalmometer permit an objective assessment of the findings. In cases where there is no ready explanation (i.e., no microphthalmos, phthisis, or history of an orbital floor fracture) an orbital imaging study is mandatory. Enophthalmos can be a sign of orbital scarring by a metastatic, sclerosing carcinoma. The latter is most commonly a carcinoma of the breast. Management is again dictated by the nature of the problem.

! Note

A pseudoenophthalmos (sometimes referred to as apparent enophthalmos) is a characteristic sign of Horner's syndrome (see Chap. 5).

Conclusion

Orbital diseases require a particularly complex differential diagnosis: aside from the customary routine tests, a detailed evaluation by a neuro-ophthalmologist is essential (with emphasis on pupillary motility, visual field examination, and tests of ocular motility). The purpose is to differentiate local ocular or orbital disorders from progressive diseases that may damage vision or be fatal.

Further Reading

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Chapter 10

Infranuclear Disorders of Ocular Motility

V. Herzau

Infranuclear disorders of ocular motility are marked by abnormal eye movements caused by lesions below the level of the cranial nerve nuclei. These lesions include damage to the cranial nerves, the extraocular muscles, or the connective tissue of the orbit. Their origins range from relatively harmless disorders to severe diseases that are life threatening. Infranuclear disorders produce paretic and/or mechanical strabismus with severe deficits of visual perception by means of diplopia (image duplication), visual confusion (image overlap), and acutely by oscillopsia (illusory movement of the environment). The principle responsibility of the ophthalmologist is to provide some symptomatic relief, determine the most likely source of the problem, and to arrange for appropriate consultation with other clinical disciplines. The search for these goals requires a thorough exploration of the history, precise measurements of ocular motility, and attention to potential accessory signs and symptoms. This diagnostic process and the specific signs and symptoms to be investigated are arranged in this chapter according to the various structural components of the neuromuscular control system governing eye movements.

Signs and Symptoms of Infranuclear Motility Disorders

Signs

Infranuclear disorders of ocular motility are caused by neurogenic, synaptogenic, or myogenic pareses. With the exception of dystrophic myopathies, only one eye is usually involved at a time, or the problem is very asymmetric, such that even a mildly reduced strength of the paretic muscle results in strabismus. More severe levels of paresis are marked by a limited range of motion and/or reduced amplitudes or velocities of saccadic movement. The angle of the deviation is variable. It increases with movement into the field of action of the paretic muscle, and decreases with movement into the field of action of its antagonist.

Pearl

This phenomenon is known as incomitance (or nonconcomitance) and is the hallmark of infranuclear paretic disease. By noting the gaze direction with the largest angle of strabismus, the examiner can identify the paretic muscle.

If, for example, a horizontal deviation increases in right gaze, accompanied by an increasing *eso*deviation, then abduction is limited in right gaze, and the abducting strength of the right eye is reduced. In the case of an increasing *exo*deviation in right gaze, however, adduction of the left eye is limited, and the paresis lies in the contralateral (left) eye. If the grouping of affected muscles is consistent with damage to a specific cranial nerve (e.g., all muscles innervated by the third cranial nerve are affected), a neuroparalytic cause of the strabismus is probable, though not proven. On the other hand, limited elevation and depression in the adducted position of an eye is more likely to be due to mechanical restriction or a myasthenic deficit of movement, since there is no selective cranial nerve paresis that can produce such a pattern.

Another hallmark of paretic strabismus is a smaller deviation when the unaffected eye is fixing (the primary deviation), and a larger angle of deviation when the paretic eye is fixing (the secondary deviation). When the eye is resting in the primary gaze position, healthy muscles receive a low and almost constant level of neural innervation from the brainstem, which gives them tonus, i.e., a steady, low level of contractile force. When the neural signal to a muscle is diminished, it produces a weaker contractile

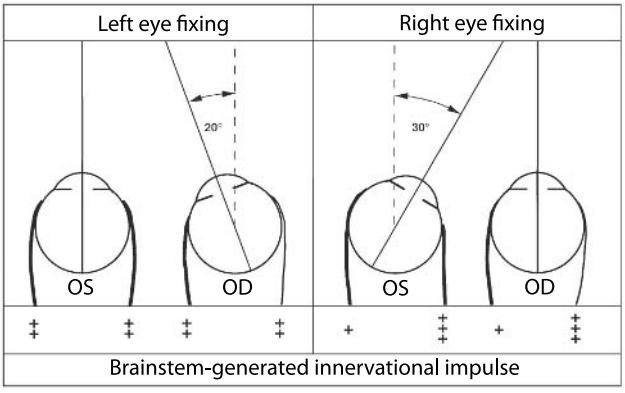


Fig. 10.1. Schematic portrayal of the primary and secondary angle of strabismus caused by an abducens paresis of the right eye when in the primary position. *Left eye fixing*: For all four horizontal rectus muscles the brainstem generates a low level neural signal (++), which serves to stabilize the horizontal positions of both eyes. If the signal to the right lateral rectus muscle is diminished or lost, the pull of the medial rectus will dominate its weakened opponent and the right eye will adopt an esodeviated position. Since the resting neural signal is small, the esodeviation will be limited in size (primary strabismic deviation = 20°). *Right eye fixing*: To stabilize the position of the right eye in the primary position, the brainstem generates a stronger signal to compensate for the paresis (+++). The same strong signal to the left eye causes a large angle of esodeviation (secondary strabismic deviation = 30°). The innervational and positional element in the *left-hand* diagram would be the same, if the right eye were fixing on an object at a 20° angle to the left. The left eye would then be held at a strabismic angle of 20°. The greater angle of strabismus when the paretic eye is fixing in the primary position reflects the paretic incomitance, which could also hold true for a myogenic or synaptogenic disorder

force, and the eye is drawn toward the field of action of the unaffected antagonist muscle. The limited innervational level in the primary position during fixation with the nonparetic eye produces a small angle of deviation in the paretic eye. Primary fixation by the paretic eye, however, requires a higher level of innervational input to maintain the position despite the relative paresis. This increased level of innervation is also sent to the contralateral eye, causing it to deviate by a larger angle, since it has normal strength and is driven by a higher level of innervation (■ Fig. 10.1).

In the opposite direction of gaze, the weakened muscle plays less of a role in maintaining eye position, the work being taken over by its antagonist. Both the primary and secondary deviation decrease with a gaze direction away from the field of action of the paretic muscle, and the smaller imbalance between the two eyes can often be compensated by the fusional vergence reflex, an involuntary visual reflex that depends on retinal image disparity as an input and then generates neural signals for vergence movements that serve to drive the eyes into alignment. Taking advantage of this phenomenon, a patient with a fresh paresis of movement and an otherwise normal capacity for binocular vision will instinctively adopt a head position that allows binocular viewing in a direction where the angle of strabismus is minimal.

Pearl

With paresis of a lateral rectus muscle, the head will be turned to the ipsilateral side, allowing binocular viewing in the contralateral field of gaze. With paresis of an oblique muscle or one of the vertical rectus muscles, one will find a corresponding extension or flexion of head position.

Symptoms

The primary symptom of paretic strabismus is binocular diplopia.

The variation in individual capacities for facultative suppression causes the diplopic symptom to be only intermittently apparent or completely unapparent for some patients, but striking apparent for others. Patients describe blurring or indistinctness of vision and a degree of photophobia or glare sensation. Only when the problem draws their full attention do they see the duplication of images. With time (weeks or months), some patients can "learn" to suppress the double image. Children acquire this sensory adaptation very quickly.

Visual confusion is a binocular symptom in which there is a perception of overlapping images, i.e., objects in differing positions in the field of view appearing in the same visual direction. Many patients cannot describe this perception very well, but if queried carefully will admit to the symptom. It is another contributor to the patient's sense of visual disorientation. Some patients will notice the loss of stereopsis, complain of problems with eye–hand coordination, and will have trouble with negotiating stairs.

If the patient fixes with the paretic eye (often the case when the paretic eye is the dominant eye), he/she will experience a sense of imbalance in which the external environment has the illusory appearance of moving. This is caused by a conflict between what the brain expects and what the eye sees. The normal coordination between eye movement and body movements has been abruptly altered. When reaching for an object or walking about while using the paretic eye, an increased effort is required to move the eye into its field of action, which in turn results in an overshoot of the arm or leg in the same direction. Conversely, eye movements in response to changes in head position (the vestibulo-ocular reflex) will be slow and incomplete, causing objects to appear to move, with the effect being greatest in the field of action of the paretic muscle. The pa-

tient will usually describe this phenomenon as dizziness. This sort of disturbance of eye–body coordination will diminish in over days or weeks, as the brain learns to compensate for viewing with the paretic eye.

Diagnostic Testing of Infranuclear Motility Disorders

History

If there is diplopia, the patient's description of the image separation can provide diagnostically valuable clues:

- When the images are overlapping, fairly close to one another, and have a constant separation that is independent of gaze direction, the problem is usually refractive in nature. It is commonly a symptom of poorly corrected corneal astigmatism, and is a common basis for monocular diplopia. The image duplication, often described as a "ghost image," will persist when the contralateral eye is closed, and will disappear when the affected eye views through a pinhole aperture (see Chap. 2).

The onset and type of binocular diplopia provide clues to the source of the problem:

- Monosymptomatic diplopia of abrupt onset is typical for ischemic neuropathies. Risk factors include diabetes mellitus, systemic hypertension, and age.
- Variable severity of diplopia that increases with fatigue is frequently the first clue that the patient has myasthenia. An associated ptosis increases the likelihood that a myasthenic disorder is in play.

When taking a history of systemic disorders, one should ask about risk factors for ischemic disease, for thyroid disease, a previously diagnosed malignancy, and for neurodegenerative disorders, such as multiple sclerosis. One should inquire about any weakness of arm or leg, problems with breathing or swallowing, and ask about paresthesias of the extremities. Often the first indication of a systemic disorder will be found in a listing of the patient's medications and a history of prior surgical procedures.

Asking about accessory symptoms helps with localizing the disorder. This is particularly true for functional deficits and pain:

- Pain on movement of the eye is characteristic of orbital myositis and of optic neuritis.
- Temporal headache on the affected side of a recent cranial nerve paresis is frequently an indication of an ischemic cranial neuropathy, but could also be a clue to the presence of temporal arteritis.

Table 10.1. Causes of painful diplopia

Orbit	Orbital myositis Invasion by sinusitis Fungal infections (e.g., mucormycosis[a]) Tumor metastases
Superior orbital fissure and cavernous sinus	Nonspecific intracavernous inflammation (Tolosa-Hunt syndrome) Nasopharyngeal carcinoma Tumor metastases Cavernous sinus fistula Cavernous sinus thrombosis
Parasellar region	Pituitary adenoma Intracavernous aneurysm Tumors (both primary and metastatic) Sphenoid sinus mucocele Petrositis (Gradenigo's syndrome)
Posterior cranial fossa	Aneurysm of the posterior communicating artery or the basilar artery
Vascular diseases	Diabetic ophthalmoplegia Giant cell arteritis Ophthalmoplegic migraine

From Glaser and Bachynski, 1990

[a] Mucormycosis is an acute, life threatening fungal infection by absidia, mucor, rhizomucor, or rhizopus. The fungus invades the respiratory or alimentary tracts, causing fungal thromboses, mural necrosis, and septic infarctions. It can be treated with voriconazole

- Facial pain suggests a lesion of the trigeminal nerve.
- Chronic pain associated with diplopia can have many causes and requires a careful, multidiscipline evaluation (■ Table 10.1).

A compensatory head posture (CHP) that has been present for a long time marks the age of an antecedent loss. A review of photos ("family album tomography") can also help to set the time of onset. Acutely developed diplopia can be a sudden decompensation of an antecedent phoria. Typical examples include congenital weakness of the superior oblique, Brown's syndrome, and Duane's syndrome (see below).

Examination

Ductions and Versions

With the patient's head held in a fixed position, the examiner observes the limits of movement of each eye during visual pursuit of the examiner's hand/finger into all diagnostic gaze positions. First, binocular movements are as-

Fig. 10.2. Schematic diagram of motility deficits. The estimates of reduced motility are symbolized by *minus signs* for each of the diagnostic gaze positions (adduction, abduction, and elevation and depression in abduction and adduction), and over actions are marked by *plus signs*. In this example, there is a marked deficit of depression in adduction in the right eye and a moderate abduction deficit in the left eye. Additional notes can be helpful, e.g., depression in adduction to midline only

sessed (versions), and if there are limitations of movement, each eye is assessed monocularly (ductions). An obvious monocular restriction can easily be seen by watching the movement of the anterior segment within the interpalpebral fissure. If the evaluation is uncertain, the corneal light reflex should be observed while the eyes are moved into the various gaze positions. The examiner holds a muscle light adjacent to his/her own dominant eye while moving around the patient, or the examiner may remain in a fixed position while the patient's head is turned. A variable eccentricity of the light reflex in one eye demonstrates a movement deficit for the corresponding gaze direction. The findings can be recorded in a simple diagram (■ Fig. 10.2). For unilateral deficits, the examiner should carefully measure the angle of the deviation in the gaze position at the maximal angle of strabismus. This method is not suitable for testing bilateral deficits, which are more readily assessed at a Goldmann perimeter. The limits of movement decrease with age.

Pearl

For older adults they are 50° for abduction and adduction, 60° for infraduction, and 40° for supraduction. If an identical pattern is found in each eye, the differential diagnosis should include a consideration of supranuclear motility deficits (see Chap. 11).

Children, uncooperative patients, and cases of supranuclear disorders can be examined by turning the patient's torso or head. The vestibulo-ocular reflex (VOR) (responsible for the so-called doll's eye phenomenon) is an involuntary reflex that cannot be suppressed. Using body or head turning movements, the examiner can determine whether a full range of movements is possible, and if so, infranuclear disorders can be ruled out.

Retraction of the globe during attempted movement into a particular gaze position suggests a mechanical component of the motility disorder. Horizontal restrictions with retraction of the globe are best detected by looking for narrowing of the interpalpebral lid fissure during the attempt. The retraction itself is best seen from the side.

Determination of the Angle of Strabismus

When determining the angular size of a strabismus, any participation of binocular fusion must be blocked. This allows measurement of the strabismus without interference from fusional vergence movements.

The examination is done with the alternating cover test, while the patient fixes attention on an object at least 3 m away. The standard gaze positions are achieved by turning the head in various directions. (For example, a head turn to the right requires the patient to fix on a position in the left field of gaze). By noting the saccadic movements with each alternation of the cover, the examiner can detect even small disparities in ocular alignment, measuring the size, as well as the type of the incomitance. Following such observations the angle of deviation can be quantified for a given gaze direction by placing corrective prisms in front of the paretic eye (the alternating prism cover test).

Subjectively, the angle of deviation can usually be determined more quickly and reliably by having the patient report the locations and separations between the doubled images. Prerequisites for this method are normal retinal correspondence, adequate visual acuity, and patient cooperation. For patients with spontaneous diplopia the motility deficit can be estimated without additional equipment during fixation on an object that has sufficient contrast with its background. For example, consider uncrossed diplopia at the primary position (the image from the right eye is seen to the right, while the image from the left eye is seen to the left) that increases in right gaze and decreases in left gaze. This means that gaze to the right produces an increasing esodeviation. To judge cyclodeviations the examiner must provide a straight line (a yardstick, for example) that the patient can use to describe the angle of tilt. The perceived image rotation is the opposite of the eye's rotation. (This is the same reversal of image direction found in horizontal and vertical strabismus). Thus, an excyclotropic right eye will see the image rotated counterclockwise, or the image seen by the left eye will appear to be rotated clockwise. Usually, the deviating eye sees the image as tilted, unless it happens to be strongly dominant.

If the doubled images are not sufficiently clear, red/green goggles can be used with a point source of light as a fixation target. The relative location and orientation of the red and green images can usually be described by patients with average cognitive skills. The contrasting colors of the two images inhibit fusion, allowing full expression of the faulty ocular alignment. This will be true for even small deviations, which would otherwise be quickly compensated by fusional vergence movements, allowing the deviation

to remain latent, rather than manifest. Additionally, the double-Maddox rod test can be used to quantify rotational disparities. Within a trial frame, a red Maddox rod is placed on the right side and a green one on the left. The orientation of the Maddox rods is set vertical, to produce horizontal lines. Parallel lines indicate no rotational deviation, while tilted lines that cross one another mark the presence of a cyclodeviation. Rotation of one or both Maddox rods to bring the lines into parallel alignment allows quantification of the cyclodeviation.

Gaze Position Tonometry

Suspicion of a restrictive disorder with intraorbital disease (e.g., Graves' disease, idiopathic myositis, foreign body, etc.) can be confirmed with gaze position tonometry. The intraocular pressure increases with maximal gaze effort in the restricted direction, if the agonist contracts and its antagonist fails to elongate. This test yields useful information only when studying clearly demonstrable restrictions of movement.

Forced Duction Testing

The restrictive component of a strabismus can be detected by means of forced duction testing. The eye is topically anesthetized and two pairs of forceps are used to grasp the conjunctiva just behind the limbus at directly opposite positions. The eye is then passively rotated in the direction of the suspected restriction and then in the opposite direction. The patient is asked to attempt movement into the restricted direction, and the contralateral eye is used to monitor the patient's ability to cooperate. Under general anesthesia, the restriction is usually much easier to detect. With local anesthesia, the examiner can also judge the contractile strength of a rectus muscle. The patient initially turns the eye away from the muscle to be tested. The two pairs of forceps are used to grasp the conjunctiva, and the patient is asked to attempt movement in the direction of interest. Normally, the examiner should feel a strong tug against the forceps. For comparison, repetition of the test in the opposite direction can help with analysis of the problem.

Fatigue and Edrophonium Tests

Suspicion of a synaptogenic paresis can be confirmed by fatigue testing. The patient is asked to maintain an ocular position that requires steady contraction of the muscle in question. Prolonged effort will amplify any myasthenic weakness, causing the strabismic deviation to increase and the strength of the affected muscle to weaken perceptibly. This will magnify a synaptogenic strabismus. Fatigue testing of the levator requires the patient to maintain a maximal upgaze position for periods of up to a full minute (Simpson test). In a healthy eye, both upper lids will remain stable in position. Myasthenic ptosis will be noticeably aggravated. A very specific test is the Cogan lid-twitch phenomenon. A myasthenic levator will over shoot its intended target. When the patient redirects gaze from an infraducted position to maximal upgaze, the lid margin will rise quickly and then fall back, sometimes over rather large distances. The resulting movement has a twitch-like appearance. It too can be magnified by fatigue.

The edrophonium test involves the intravenous injection of 0.5 to 0.8 mg of edrophonium chloride, following a test dose of 0.2 mg. A syringe with 1 ml of 1% atropine is kept at hand, allowing rapid reversal of the cholinergic effect, if needed. The test is most useful when an easily demonstrated weakness is evident. Rapid and strong, temporary reversal of a manifest weakness is diagnostic of a myasthenic disorder. A more sensitive method involves intravenous administration of the edrophonium while simultaneously recording a tonographic tracing. A positive response is seen as an increase in the tone of all of the extraocular muscles, causing an abrupt rise in intraocular pressure that creates a step-like discontinuity in the tracing.

! Note

In addition to the results of these tests, the following are also helpful:

- An unambiguous test for myasthenia is the determination of serum titers of acetylcholine receptor antibodies. It is highly specific, but only marginally sensitive. Positive results are present in about 50% of cases.
- The Tensilon test can also be negative in the presence of known myasthenia. For cases that remain in question, repeated testing at intervals of several weeks will occasionally confirm the diagnosis.
- The presence of a myasthenic state does not rule out other possible causes of oculomotor paresis, such as a sphenoid wing meningioma.
- There is a statistical association of Graves' disease with myasthenia, and both restriction and paresis may be simultaneously present, resulting in highly variable test results that are very difficult to interpret.
- Occasionally, a myasthenic strabismus can be the presenting sign of a (potentially malignant) thymoma.

Video 10.1

Neurogenic Oculomotor Paralyses

Definition

Neurogenic oculomotor paralyses are third, fourth, and/or sixth cranial nerve palsies. They can be recognized by their characteristic patterns of motor deficits, by the incomitant nature of the strabismus, and the usual absence of mechanical restriction, myopathy, myasthenia, or orbital disease.

Supranuclear disorders must be ruled out, if the motility deficit is not typical of cranial nerve disease (e.g., skew deviation, asymmetric gaze palsies, or internuclear ophthalmoplegia; see Chap. 11). Nystagmus, saccadic pursuit movements, bilaterality, and elimination of the motility deficit by VORs, convergence movements, or Bell's phenomenon, all suggest a supranuclear source of a motility deficit.

After determination of a cranial neuropathy, the clinician should search for any other evidence of neural deficits whose anatomic structures lie adjacent to the damaged nerve. If the primary lesion is located at or above the exit of the paretic nerve from the brainstem, there will often be fascicular syndrome with deficits in the adjacent long tracts. Combinations of neurogenic oculomotor pareses with deficits in the ophthalmic division of the trigeminal nerve indicate a lesion in the cavernous sinus. For more anteriorly located lesions, such as in the superior orbital fissure or the orbital apex, there will usually be signs and/or symptoms of orbital disease, often with damage to the optic nerve.

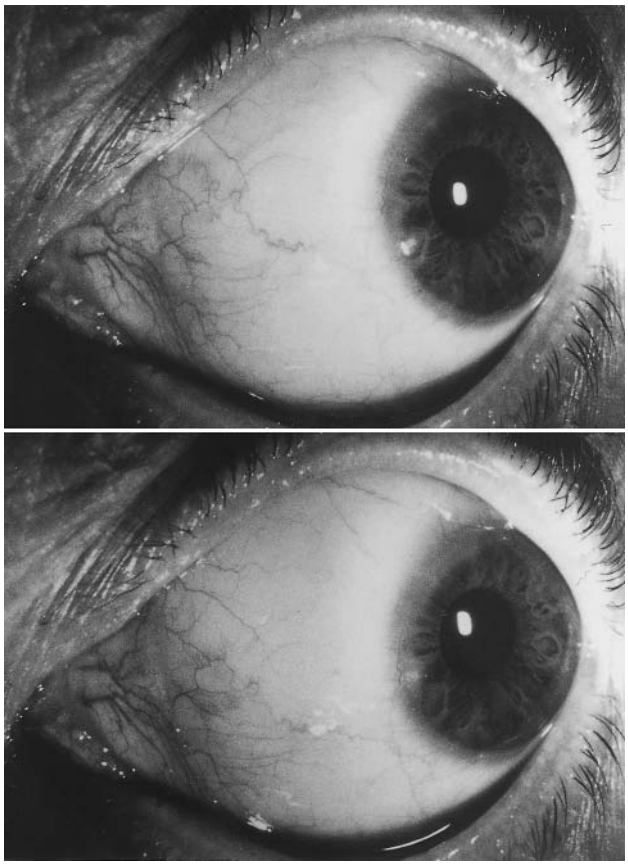


Fig. 10.3. Oculomotor paralysis of the left eye with retained trochlear function. *Top* Attempted elevation, *bottom* attempted depression. The incyclotorsion of the globe with attempted depression is evident in the changed positions of the conjunctival vessels

Oculomotor Nerve Paralysis

As a single cranial nerve, the oculomotor nerve supplies innervation to the medial rectus, inferior rectus, inferior oblique, superior rectus, and the levator palpebrae. It also contains the parasympathetic supply to the internal ocular smooth muscle tissues of the pupillary sphincter and the ciliary body.

Clinical Findings

Total loss of function in the third cranial nerve produces paralysis of the levator palpebrae superioris, with complete ptosis of the upper lid. The sympathetically innervated smooth muscle of the upper lid (Müller's muscle) can shorten the levator aponeurosis but will not cause any opening of the palpebral fissure. With passive elevation of the upper lid, the examiner will find the eye resting in an abducted position of 20 to 30°. Attempts at adduction in fresh cases will produce a weak movement toward, but not all the way to, the primary position. Cases that are more chronic will stop the adducting motion even more short of the primary position. Elevation and depression will be completely absent. (If the trochlear nerve is spared, attempts at downgaze will cause an incyclotorsional movement (■ Fig. 10.3).

If there is also an internal ophthalmoplegia, there will be a paretic mydriasis, pupillary sphincter paralysis, and an anisocoria that increases in bright light surroundings, and a paralysis of accommodation.

With subtotal damage of the third cranial nerve, several patterns of paresis can appear:

- External ophthalmoplegia: Only the extraocular muscles are affected. (Usually called a pupillary-sparing third nerve palsy.)
- Internal ophthalmoplegia: Only intraocular muscles are affected.
- Complete external and/or internal oculomotor paralysis: The function of all external or internal ocular muscles has been lost.

Video 10.2 Video 10.3 Video 10.4

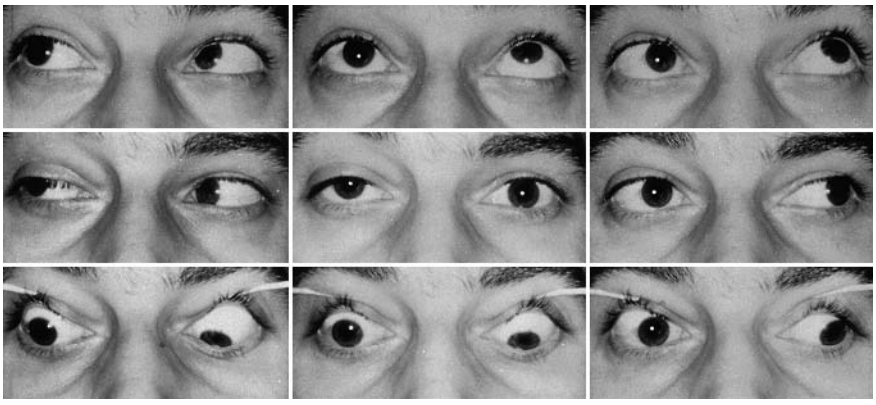


Fig. 10.4. Gaze-direction photos of a partial internal and external ophthalmoplegia in the right eye: Upper lid movement, elevation, depression, and adduction are all limited, but not completely gone

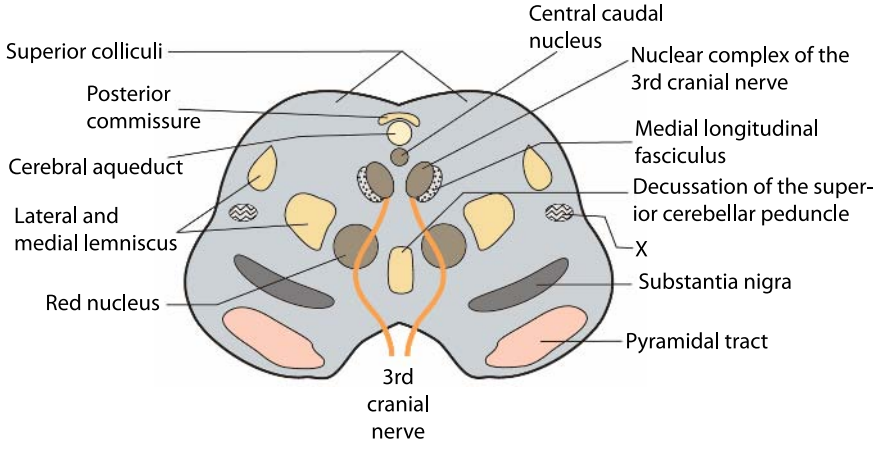


Fig. 10.5. Schematic section through the rostral midbrain at the level of the oculomotor nuclei. *X* probable location of the sympathetic tract

Table 10.2. Brainstem syndromes with fascicular oculomotor pareses

Name	Affected structures	Associated brainstem signs and symptoms
Weber's syndrome (third nerve palsy with contralateral hemiplegia)	third nerve, pyramidal tract	Contralateral hemiparesis
Nothnagel Claude's syndrome (inferior red nucleus syndrome)	Red nucleus, superior cerebellar peduncle (brachium conjunctivum)	Contralateral ataxia, rubral tremor
Benedikt's syndrome	Red nuclei, substantia nigra	Contralateral ataxia, contralateral hemichorea

- Incomplete external and/or internal oculomotor paralysis: Not all muscles innervated by the third nerve are paralyzed. ■ Figure 10.4 illustrates a patient with a partial oculomotor paralysis.

Fascicular Paralysis of the Oculomotor Nerve

Due to the separation of the third nerve fascicles as they leave their nuclear complex, pass through the red nucleus, substantia nigra, and the pyramidal tracts to exit the brainstem into the interpeduncular fossa, damage in this region often results in incomplete paralysis. The pupil may be spared, or an isolated paralysis of elevation may be found. Even patterns of isolated superior or inferior divisional palsies of the third nerve can arise from disease located within the midbrain. Associated deficits of additional midbrain structures are likely to be found, including vertical gaze pareses (damage to the rostral interstitial nucleus of the medial longitudinal fasciculus), bilateral ptosis (typically present with lesions of the third nerve nucleus), paralysis of convergence and/or accommodation, and loss of all contralateral somatic sensation (■ Fig. 10.5 and ■ Table 10.2). The classical brainstem syndromes listed in ■ Table 10.2 do not usually occur in isolation but are accompanied by loss of function in other neighboring structures. Definitions given in the published literature on this subject are correspondingly imprecise. Most fascicular pareses are ischemic in origin, and are only occasionally the result of infiltrating of inflammatory processes.

Subarachnoid Damage to the Oculomotor Nerve

From the ventral midbrain, through the interpeduncular fossa and to its entry into the cavernous sinus, the third nerve lies in the subarachnoid space, where it is exposed to hemorrhages from aneurysms arising from the supraclinoid carotid artery, mostly at the exit of the posterior communicating artery. Rupture of such an aneurysm produces paralysis of the third nerve, but also the dramatic symptoms of acute subarachnoid bleeds, including abrupt headache of the worst sort, reduced levels of consciousness up to complete coma, and pronounced meningismus. The ophthalmologist will not be confronted by this syndrome in his/her own office.

! Note

In about one third of cases the course is more gradual, beginning with an incomplete internal and external oculomotor nerve paralysis, which precedes onset of extreme levels of head pain referred to the orbital apex. The ocular presentation may lead the patient to consult the ophthalmologist, who should then immediately arrange for emergent neuroradiologic study. Only a few days following such a presentation can one expect an abrupt subarachnoid hemorrhage, a frequently fatal event that can be avoided with timely surgical management of the aneurysm.

Other causes of damage to the subarachnoid portion of the oculomotor nerve include severe head trauma, in which the nerve can suffer a contusion or traction injury. A posttraumatic supratentorial hemorrhage can also lead to a secondary oculomotor nerve paralysis, in which ventral displacement of the brainstem causes a compression of the nerve on fixed structures at the skull base. Another mechanism for the same type of injury is a space-occupying supratentorial process (hemorrhage, tumor) that causes the uncus to herniate, compressing the third nerve against the margin of the tentorium. This type of paralysis begins with an ipsilateral pupillary mydriasis (Hutchinson's pupil). If the process is not controlled, it leads to loss of consciousness and an external ophthalmoplegia.

! Note

When mild head trauma is followed by an oculomotor nerve paresis, it suggests antecedent damage to the nerve, such as by tumor or aneurysmal compression, and requires neuroradiologic imaging.

Intracavernous Lesions of the Oculomotor Nerve

All ocular efferents and the first two divisions of the trigeminal nerve course through the cavernous sinus. If the lesion producing an oculomotor paresis lies in this region, there are usually additional deficits affecting the adjacent nerves.

Orbital Lesions of the Oculomotor Nerve

Lesions in the orbit that damage the third nerve are usually accompanied by signs of inflammation and exophthalmos that allow for rapid identification of the locus of disease. Usually, ocular movements are also affected by mechanical restriction or myogenic factors, such that an isolated pattern of cranial nerve disease is not apparent. Depending on the locus of disease, other cranial nerves can suffer collateral damage within the orbit. Isolated loss of the superior or inferior division of the oculomotor nerve is not by itself evidence for disease within the orbit, since the corresponding functional/anatomic separation of fibers is maintained along the entire length of the third nerve.

● Pearl

Solitary infiltrating metastases (e.g., carcinoma of the breast or stomach) often cause a fibrotic contracture of the orbital tissues. A common presentation is enophthalmos with chronic conjunctivitis and severely restricted ocular motility with both neurogenic and myogenic components. Thin-section CT scans of the orbit with contrast are sufficient to make the diagnosis. The mechanical restriction of motility is easily confirmed by forced duction testing (see also Chap. 9).

Microvascular Oculomotor Pareses

Microvascular ischemia of the oculomotor nerve arises from small-vessel disease of the vasa vasorum supplying the third nerve. It is the most common cause of oculomotor paresis in most ophthalmic practices. Though not specific, the presentation is characteristic, including acute onset of diplopia, complete or partial palsies of the muscles supplied by the third nerve, sparing of the pupillary sphincter, and ipsilateral retrobulbar and/or temporal pain. The pain is thought to stem from the acute inflammatory response to the infarcted nerve within the subarachnoid space, i.e., a locus of sterile meningitis. The pupillary sparing reflects the surface location of the autonomic fibers, providing some oxygen supply via the cerebral spinal fluid. The fibers are also small and have lower metabolic requirements than the larger, more quickly conducting oculomotor fibers. It also explains their greater susceptibility to compressive lesions (see Chap. 5, Fig. 5.6 c).

Simultaneous damage to the sympathetic fibers in the cavernous sinus can also conceal damage done to the pupillomotor fibers by minimizing the resultant mydriasis.

Vasculopathic oculomotor cranial nerve palsies are most common in middle-aged and elderly patients. The paresis is monocular, and typically, other cranial nerves are not affected. A spontaneous recovery is the rule, taking 4 to 6 months for completion. The diagnosis can initially be difficult. During the first 10 days, there may be a staircase progression of additional motor loss, which happens in more than half of all cases. Risk factors for this type of small-vessel disease include age, diabetes mellitus, hypertension, and generalized arteriosclerosis.

Relapses in the same or other ocular motor nerves are not uncommon. More than one nerve can be involved at the same time and problems can appear bilaterally, but these are uncommon events. The diagnosis is difficult to confirm initially, but it is ultimately proven by the subsequent recovery.

! Note

Even the classic presentation of a total third nerve palsy with pupillary sparing in elderly patients can in exceptional cases be the first hint of an arterial aneurysm. A decision to omit neuroradiologic imaging must be made with provision for adequate monitoring of the patient's clinical signs during the acute phase.

Uncommon Types of Oculomotor Pareses

Ophthalmoplegic Migraine

A small number of migraine patients experience an ipsilateral oculomotor paresis in connection with an episode of migraine. Like the migraine attacks, this form of paresis appears during childhood as the initiating event in an episode that includes vomiting, photophobia, abdominal pain, irritability, and (less commonly) headache.

The paresis affects all branches and recovers completely, as a rule, within a month's time. Relapses can repeatedly occur, sometimes after years of inactivity, and such repetition can produce some degree of permanent paralysis. The diagnosis is suggested by the typical course with a positive family history, which J.S. Glaser found in 90% of pediatric cases. Since many organic disorders can produce a similar presentation, children with attacks like these should have at least one MRI study to rule out other disorders.

Oculomotor Pareses in Children

Monosymptomatic oculomotor paralyses during childhood are uncommon. One half of pediatric third nerve pareses are congenital, and are often associated with signs of aberrancy (synkinesis). In individual cases, the cause usually remains unknown. Frequently, a congenital oculomotor paralysis will have recurrent periods of spasms lasting about one minute, usually recurring with a regular frequency (cyclical oculomotor paralysis).

The most striking sign is seen at the onset of a cycle, with a vertical twitching of the ptotic upper lid. The lid then lifts and the mydriatic pupil constricts. Shortly after that, the signs will fade and disappear in an order that reverses their onset.

Acquired oculomotor pareses in childhood are mostly traumatic, the consequence of frequent migraine episodes, associated with tumors, or in the context of acute meningitis. Aneurysms as a cause of oculomotor paresis are a rarity in children. An acquired, nontraumatic paresis in a child requires an MRI study with contrast enhancement. If meningitis is suspected, a lumbar puncture is indicated. Depending on the child's age, evaluation to rule out or treat amblyopia in the affected eye is necessary

Aberrant Regeneration of the Oculomotor Nerve

A common phenomenon in disease of the third nerve is called aberrant regeneration. The precise mechanism by which this occurs is not know, but it appears almost exclusively in company with mechanical injury to the nerve, whether by trauma or direct compression of the nerve by a tumor or aneurysm. It is rare to find this phenomenon associated with small vessel disease of the third nerve. Since the oculomotor nerve serves several muscles, regenerating axons, starting from the site of the injury, reinnervate not just their respective native muscles but also several muscles, which is one postulated mechanism for this phenomenon.

The aberrant movements appears about 2 months after the damage to the nerve, typically with recovery of the ptosis and a decrease in the divergent strabismus. The loss of elevation and depression does not usually recover, such that a useful field of binocular single vision does not return. A common and dramatic pattern of aberrancy is contraction of the levator on attempted infraduction (called the pseudo–von Graefe sign). Even the pupil's movements and accommodation can vary with changes in gaze position. Persistent palsies and varying degrees of re-innervation produce a highly variable range of possible outcomes that are essentially unpredictable.

● Pearl

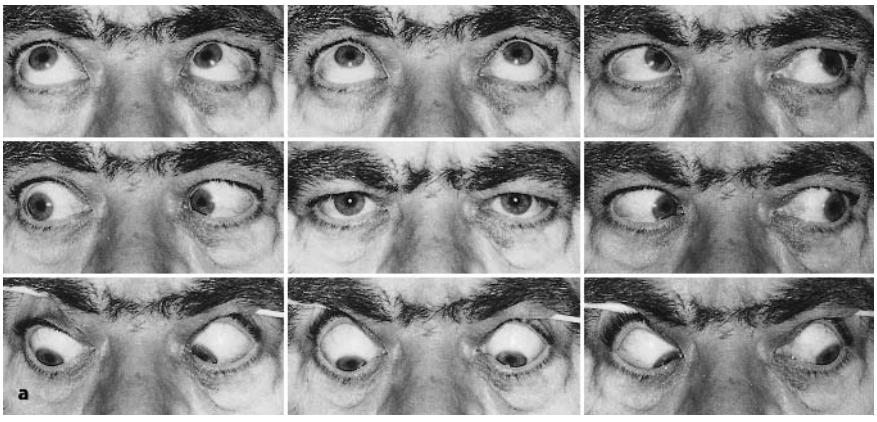
Primary aberrancy, i.e., synkinetic movements without prior acute paralysis of the oculomotor nerve, can develop as a complication of a chronic insult to the nerve, typically compression by a meningioma or an aneurysm in the cavernous sinus.

Video 10.5

Video 10.6

Video 10.7

Video 10.8



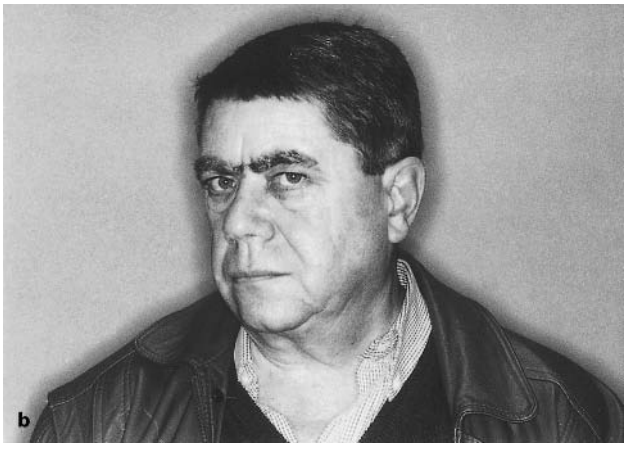


Fig. 10.6. **a** Gaze direction photos of an incomplete paralysis of the right abducens nerve. The abduction of the right eye is limited. On fixing an object at near, the ocular alignment is normal. **b** A compensatory head turn to the right is necessary, so as to avoid uncrossed diplopia when viewing distant objects

The regeneration of oculomotor nerves damaged by meningioma in some cases can restore normal motor function, sometimes leading to a misdiagnosis of a microvascular event.

Abducens Nerve Paralysis

Clinical Presentation

Paralysis of the sixth cranial nerve causes an abduction deficit with a nonconcomitant esotropia and uncrossed binocular diplopia that increases with attempted gaze to the ipsilateral side. With partial paralyses, single binocular vision can be retained by turning the head to the ipsilateral side, to avoid the field of action of the paralyzed muscle (CHP), and binocular single vision is often retained at reading distances (■ Fig. 10.6). Older patients who have an exophoria at near and who are accustomed to making only small shifts of gaze direction may notice the diplopia only when looking out of a window or when riding in a car.

Pearl

Small bilateral abducens palsies without an obvious abduction deficit can produce a concomitant esotropia that is present at distance, but not at near. A similar problem among elderly patients is abrupt in onset, not associated with any other signs of disease, and is sometimes called divergence paresis esotropia. The distinction between these two is difficult to make. If MRI or CT scans show no sign of disease and the problem is stable, good relief of the diplopic can be had with the use of base-out prism glasses.

Fascicular Abducens Palsies

The anatomic neighbors of the paramedian pontine reticular formation (the PPRF, also the center for horizontal gaze control) include the facial nerve, the (uncrossed) pyramidal tracts, the sensory and sympathetic long tracts, and the abducens nerve (■ Fig. 10.7). The clustered proximity of these structures and the long intrapontine course of the sixth cranial nerve make collateral damage very common for fascicular lesions of the abducens nerve (■ Table 10.3). The classical brainstem syndromes described in the nineteenth century literature are seldom seen in isolation. The accessory or collateral symptoms associated with damage to the sixth nerve provide invaluable clues to the topographic clinical diagnosis of fascicular sixth nerve palsies. Monosymptomatic fascicular palsies are found in association with microvascular or demyelinating disorders, but are not associated with other diseases.

Video 10.9 Video 10.10 Video 10.11

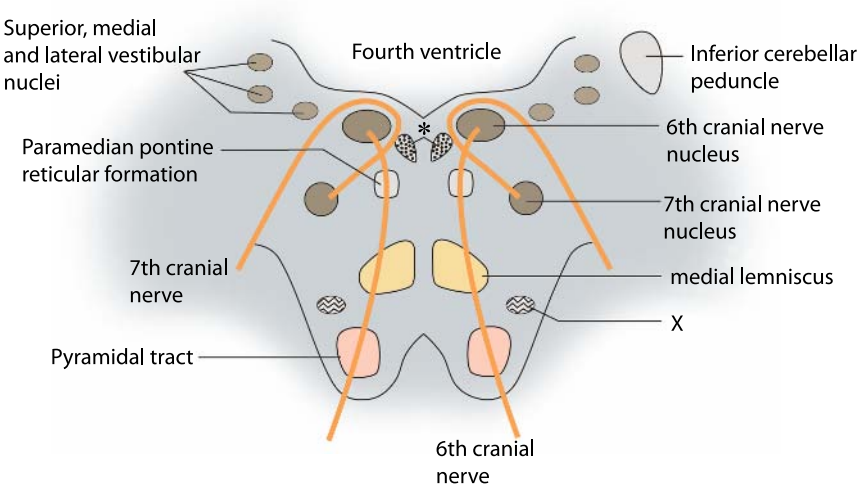


Fig. 10.7. Schematic section through the pons at the level of the abducens nuclei. The paths of the fascicles of the sixth and seventh cranial nerves are diagrammed to show the internal genu of the facial nerve. *Medial longitudinal fasciculus; *X* probable location of the sympathetic tract

Table 10.3. Brainstem syndromes with fascicular abducens pareses

Name	Affected structures	Associated brainstem signs and symptoms
Gasperini's syndrome (pontine tegmental syndrome)	PPRF, seventh nerve, (trigeminal and vestibular neurons), medial lemniscus, spinothalamic tract	Ipsilateral: gaze palsies, fifth, seventh, and eigth nerve pareses Contralateral: sensory loss
Cestan Raymond syndrome	cerebellar peduncles; corticospinal tract; medial lemniscus	Ipsilateral: cerebellar ataxia Contralateral: hemiparesis, hemihypesthesia
Foville syndrome	Facial nerve nucleus, (trigeminal neurons, ciliospinal tract); corticospinal tract	Ipsilateral: seventh nerve paresis (fifth nerve component), Horner's syndrome Contralateral: hemiparesis
Millard Gubler syndrome	Facial nerve nucleus; corticospinal tract	Ipsilateral: facial palsy; Contralateral: hemiparesis

PPRF Paramedian pontine reticular formation

Abducens Pareses Caused by Lesions in the Subarachnoid Space and at the Petrous Apex

The sixth nerve is fixed in position at its exit site from the brainstem, located at the inferior border of the pons, and at its entry into the dura of the clivus. Caudal displacement of the brainstem can result in bilateral traction injuries of the sixth nerves as a nonspecific sign of a distantly located, space-occupying disease (supratentorial masses, hemorrhages, or edema, variations in intracranial pressure following lumbar puncture, and idiopathic intracranial hypertension [IIH]). While still in the subarachnoid space or shortly after its entry into the dura, the sixth nerve passes in close proximity to the apex of the petrous bone, the facial nerve, and the trigeminal nerve. Paramastoid inflammatory disease and tumors of the petrous apex produce Gradenigo syndrome, a sixth nerve palsy accompanied by a deep, boring pain that radiates to the brow and temples. Nasopharyngeal carcinomas that have eaten through the clivus can produce an identical set of symptoms. They can also invade the pterygopalatine fossa, producing dysesthesias and loss of sensation in the tissues innervated by the infraorbital nerve (Behr's syndrome).

Crushing injuries of the skull with horizontal compression can cause petrous bone fractures with abducens and facial nerve palsy and hemorrhaging from the external auditory canal.

Pearl

The long intracranial course of the sixth nerve makes it vulnerable to both space-occupying and meningitic inflammatory disease.

Abducens Palsies Caused by Intraorbital Disease

With its short course through the orbital apex, damage to the sixth nerve by orbital lesions is invariably accompanied by other neurological deficits and structural alterations of the orbital tissues. These include damage to the optic nerve, the third, fourth, and fifth cranial nerves and/or orbital signs of proptosis, enophthalmos, globe displacement, and mechanical restriction of ocular movements.

Microvascular Sixth Nerve Palsy

Spontaneous palsies of the abducens nerve that are not associated with signs of damage to other neighboring structures are common. A microvascular pathogenesis (loss of arteriolar/capillary blood supply to the nerve) is probable, when the patient is more than 50 years old, or has known vascular disease (hypertension, diabetes mellitus, generalized arteriosclerosis), has no simultaneous, associated deficits, and recovers the lost sixth nerve function within 3 months.

Benign Pediatric Sixth Nerve Palsy

Isolated, unilateral abducens pareses that recover in 3 or 4 weeks can develop in children during recovery from viral or bacterial infections. Given the high frequency with which monosymptomatic sixth nerve palsies are caused by tumors, a benign etiology cannot be assumed without first obtaining an MRI scan and then following the patient's subsequent recovery on a weekly basis.

Congenital Sixth Nerve Palsy

Isolated, congenital sixth nerve palsies are very uncommon and recover spontaneously within 6 weeks.

Most congenital abducens pareses are found in association with other neurological disorders, such as Möbius' syndrome or Duane's syndrome.

Möbius' Syndrome

Möbius' syndrome is a combination of a nuclear sixth nerve paresis (a horizontal gaze palsy with retained convergence) and a nuclear paresis of the facial nerve. The facial muscles are atrophic; lagophthalmos puts the corneas of both eyes at risk. Usually both sides are affected. The causes are heterogeneous (developmental disorders, hypoxia, or toxic damage). Other neurological problems are frequent.

Duane's Syndrome

Duane's syndrome is also associated with hypoplasia or aplasia of the abducens nerve nucleus. The internuclear neurons, however, are spared. The lateral rectus muscle is innervated by aberrant medial rectus axons originating in the third nerve nucleus. Attempted adduction produces a co-contraction of the medial and lateral recti, with an adduction deficit and retraction of the globe, producing a narrowing of the interpalpebral fissure. Depending on the extent of the hypoplasia and the variably aberrant innervation, three basic forms of Duane's syndrome have been defined by Huber:

- Type I: a marked abduction deficit, a mild adduction deficit, and retraction
- Type II: primarily an *ad*duction deficit with marked retraction
- Type III: severe abduction and adduction deficits

Most of the cases seem sporadic and are unilateral. Most of them arise without any explanation for their development, and the left eye and female sex are the more severely affected. Type I occurs most frequently. Characteristically, and despite a total absence of abducting movement in the affected eye, binocular vision with stereopsis is usually present in the motor hemifield on the unaffected side.

A compensatory head turn is the rule. Additional sensory deficits of the associated strabismus and refractive amblyopia frequently occur and should be managed appropriately. The motility deficit remains unchanged throughout the patient's life, and surgical attempts are indicated in cases of severe head turn.

Differential Diagnosis of Sixth Nerve Pareses

A number of diseases should be considered in the differential diagnosis of a sixth nerve palsy.

Graves' Disease

A history of prior problems with hyper- or hypothyroidism may suggest an acquired restrictive mechanism, and if Graves' disease has been active in the past, there should be some evidence of proptosis, conjunctival erythema, chemosis, or lid retraction. Forced duction testing (see above) will demonstrate restriction of movement, the intraocular pressure will rise with attempts to move the eye into the restricted field of gaze, and CT/MRI/ultrasound testing will confirm the presence of rectus muscle thickening (see Chap. 9).

Idiopathic Orbital Myositis

Orbital myositis usually presents with lid swelling, regional conjunctival hyperemia overlying an affected rectus muscle insertion, and pain on eye movement. Decreased elasticity of an affected temporal rectus will also cause adduction movements to be restricted as well. CT/MRI scans demonstrate marked thickening of the affected muscle(s), with extension of the inflammatory process from the muscle belly to the tip of its tendinous insertion. Relapses can affect the same or other muscles, sometimes several at a time. A prompt response to corticosteroid therapy with rapid improvement in all symptoms is pathognomonic of the disorder. A common starting dose is 1 mg of prednisone for each kilogram of body weight. After complete clinical suppression of findings, a slow taper of the drug is instituted. If the myositis recurs, another course of the same therapy is used. For a third episode (second relapse), the use of orbital irradiation is recommended (see Chap. 9).

Video 10.12

Ocular Myasthenia

Ocular myasthenia should be considered when there is a history of ocular or general problems with fatigue, frequent variations in the size of a strabismus, an earlier episode of diplopia or ptosis, or signs of ocular muscle fatigue. A normal pupillary response to light and accommodation, a positive edrophonium test, and no restrictions found when testing forced ductions are all clues to a myasthenic process. Antibodies to acetylcholine receptors in the serum establish the diagnosis incontrovertibly.

Spasm of the Near Reflex

Spasms of accommodation and convergence are usually functional in nature, but are occasionally the result of a severe head injury or part of a dorsal midbrain syndrome. A highly variable (moment-to-moment) esotropia is accompanied by pupillary miosis and accommodative myopia. When binocular horizontal pursuit movements are tested, the adducting eye takes up fixation in either direction. This pseudo–abducens palsy is usually enhanced during cover/uncover testing (■ Fig. 10.8). The spasms can last for a few seconds or for several hours. In addition to the blurring and diplopia, headache is associated with the longer lasting spasms.

Pseudoabduction Deficit

An abduction deficit in children with infantile esotropia can be confused with a sixth nerve paresis. The patient's history, latent nystagmus, and a full range of abducting movements during vestibular stimulation all suggest that an abducens weakness is not involved. Vestibular stimulation is best done by holding the child aloft. If still in doubt, the physician can use temporary monocular patching while observing the behavior of the uncovered eye.

! Note

Infantile esotropia does not prevent sixth nerve palsies.

A large esophoria will decompensate into a manifest esotropia when there is a loss of vision in one eye. This sort of presentation will be associated with an afferent pupillary defect as a part of a retinal and/or optic nerve disorder, but can also be the result of a dense monocular clouding of the optic media. It will simulate an abduction deficit in the eye with visual loss. The undamaged eye will take up primary fixation, and pursuit of movement toward the affected side will commonly induce a head turn at the far end of the movement, as the patient compensates for a masking of the target by the bridge of the nose.

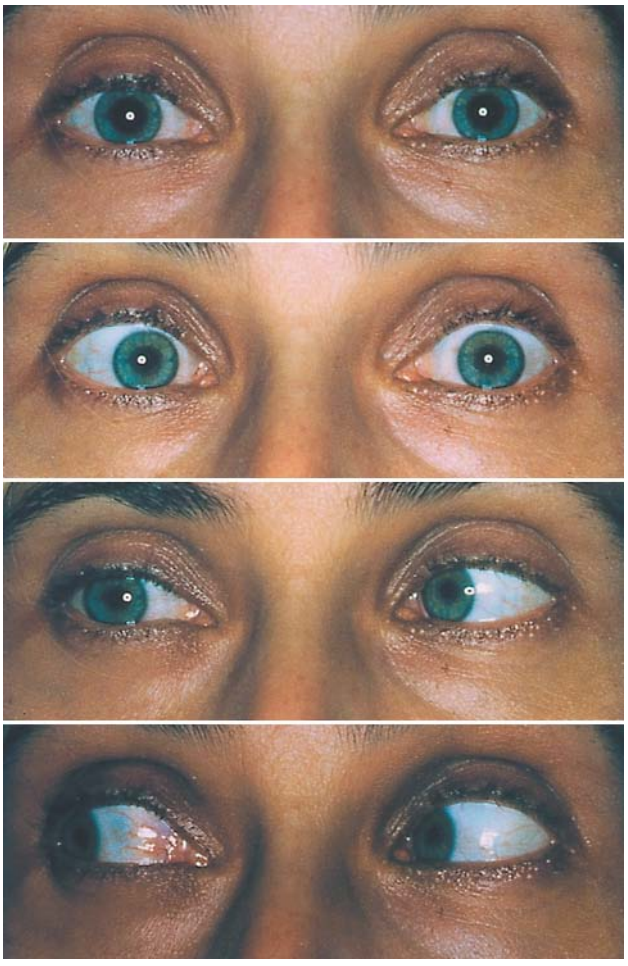


Fig. 10.8. Intermittent spasms of the near reflex. *First image (top)* Normal eye positions, pupils at mid-dilation, normal acuity. *Second image* Sudden onset of a right esotropia, pupillary miosis, blurred vision. *Third image* At right gaze position the left eye takes up fixation, and right eye appears to have abduction deficit. *Fourth image* After encouraging maximal gaze effort to the right, or after brief occlusion of the adducting eye, the right eye is shown to have a normal range of abduction

Trochlear Palsies

Clinical Presentation

A lesion of the trochlear nerve will cause a loss of depression in adduction with a vertical separation of doubled images that increases in downgaze and on gaze to the contralateral side (■ Fig. 10.9). The depression deficit is frequently not obvious, when examining duction and version movements, but with cross-cover testing, the deficit is immediately recognizable. Since the superior oblique muscle intorts, depresses, and (weakly) abducts the affected eye, the diplopia seen in downgaze shows a downward displacement and a prominent tilt of the image from the strabismic

Video 10.13

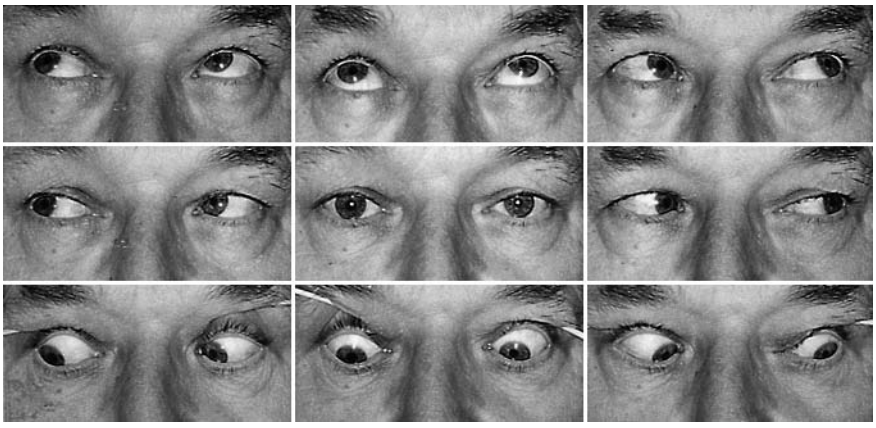


Fig. 10.9. Gaze direction photos of a paresis of the left trochlear nerve. Depression of the left eye is reduced in adduction. The hypertropia of the left eye in the right gaze position is evident, but it vanishes on upgaze to the right. Loss of the abducting effect of the superior oblique causes a small esodeviation in downgaze

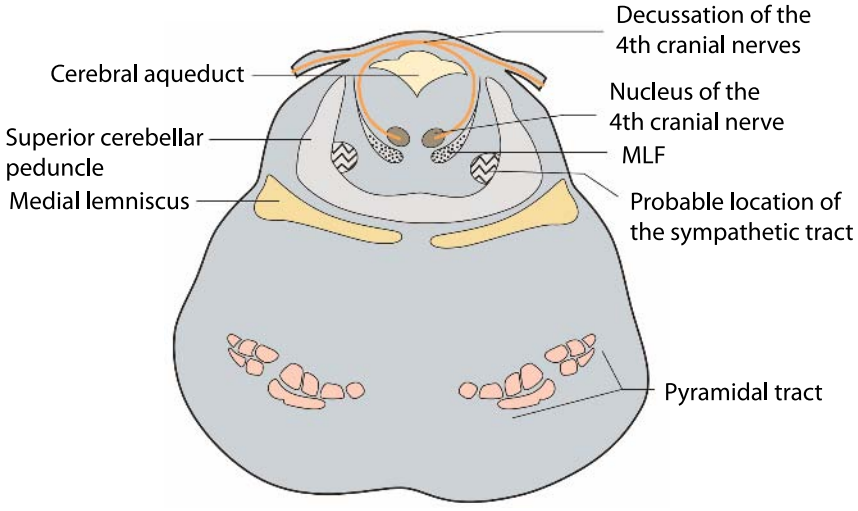


Fig. 10.10. Schematic cross section through the caudal midbrain at the level of the fourth cranial nerve nuclei. *MLF* Medial longitudinal fasciculus

eye. The excyclotorsion of the paretic eye increases in downgaze, causing an apparent upward tilt of the temporal end of a contour. Such forms of diplopia do not benefit from prism therapy.

Pearl

Bilateral symmetrical paralysis of the fourth nerves will have no vertical disparity of eye or image position, but the excyclorotation in both eyes produces a very large torsional displacement of images. The patient will complain about the tilting of images, especially while trying to read. Some patients can eliminate this type of diplopia in an extreme upgaze position, which can lead to a compensating head posture with the neck flexed and the chin against the chest wall (involuntarily demure).

With unilateral trochlear palsies, the compensating posture will have the head bowed, and turned and tilted toward the contralateral side. Conversely, tilting of the head toward the affected side will cause the eye to attempt an incyloduction movement. This movement requires the simultaneous contraction of the superior oblique and the superior rectus. If the oblique is weak, the unopposed superior rectus contraction produces an ipsilateral hyperdeviation. Tilting of the head to the opposite side will conceal the deviation, making fusion of images possible. This in turn leads to a CHP with tilting to the side away from the paretic superior oblique. For those with developmental weakness of the superior oblique (a developmental anomaly of a long, floppy trochlear tendon that reduces its mechanical advantage), old photos will often show a head tilt during childhood.

Fascicular Paresis of the Trochlear Nerve

A distinction between nuclear and fascicular pareses of the fourth nerve cannot be made based on clinical symptoms and signs, since all lesions of the caudal midbrain tectum affect both the nucleus and the very short fascicles of the trochlear nerve. Space-occupying lesions in the caudal midbrain tectum are nearly always accompanied by other brainstem signs and symptoms. Lesions in the dorsal tectum produce uncrossed deficits, while lesions in more rostral locations will cause crossed deficits (■ Fig. 10.10).

Video 10.14

The common bilaterality of traumatic trochlear nerve palsies is explained by injury to the fascicles in the anterior medullary velum, at the site where both nerves decussate. The mechanism of the trauma is one of stretching of the fascicles, as a distant effect of closed head injuries. A combined fourth nerve paresis with a contralateral Horner's syndrome is another, though less common, result of injury in this region, where the descending sympathetic tract is located close the fascicles prior to their decussating.

Subarachnoid Trochlear Pareses

Despite the long course of the trochlear nerve in the subarachnoid space, there are no typical clinical signs for a lesion of the nerve in this region. The trochlear nerve is very thin and highly sensitive to compression and stretch injuries at its exit site on the dorsal side of the brainstem. In the absence of signs arising from neighboring structures, a precise localization of the lesion is not possible without a neuroradiological imaging procedure.

Acquired, Isolated, Unilateral Trochlear Pareses

Trochlear palsies of this sort in most cases must be attributed to a microvascular pathogenesis. This is consistent with their abrupt onset and their associated risk factors, such as diabetes mellitus, age of 50 or more, hypertension, and generalized arteriosclerosis. In most cases, the cause cannot be proven. A general medical exam to look for unsuspected hypertension or threshold diabetic states is indicated. Usually the problem resolves spontaneously within about 3 months. If it does not recover or is joined by additional signs and symptoms, a more thorough investigation is needed, and should include an MRI of the brain and a lumbar puncture.

Pearl

For the causes of an isolated, acquired trochlear paresis a rule of 10-20-30-40 is used: 10% neoplasms/aneurysms, 20% ischemic, 30% undetermined or very unusual causes, and 40% traumatic.

Differential Diagnosis of Trochlear Nerve Pareses

In many cases of superior oblique paresis, it is not the trochlear nerve at fault, but it is instead caused by changes in the trochlear tendon complex or the body of the muscle itself. These patients have a marked overaction of the antagonist inferior oblique in adduction, a positive Bielschowsky head-tilt test, an amazing amplitude of the vertical fusional vergence movements (able in some cases to fuse a hyperphoria of 40 prism diopters), and a long standing history of head tilt to contralateral side of the affected eye (look at old photos). Intraoperatively, the superior oblique tendon can be drawn way out of the orbit with a muscle hook (this is not the case with trochlear nerve palsies), or one find a hypoplastic, very thin tendon. Orthoptic evaluation finds no indication of paralysis, since the angle of vertical strabismus is constant in both upgaze and downgaze to the contralateral side. In other cases that are otherwise identical, a truly paretic incomitance can be found. With CT or MRI scanning of such cases one usually finds a hypoplastic superior oblique muscle. The very large fusional vergence amplitudes can spontaneously or following minor injuries have a very sudden decompensation with diplopia, mimicking an acquired paresis of the trochlear nerve.

Other differential diagnoses of trochlear paresis include:

- Trochlear tendon injuries (often with mechanical restriction of elevation in adduction, much like that of Brown's superior oblique tendon sheath syndrome)
- Elevation deficit in abduction of the contralateral eye (e.g., in patients with asymmetric Graves' disease and fibrotic contracture of the inferior rectus)
- Myasthenia (fatigue phenomenon, positive edrophonium test)
- Skew deviation (rather than an excyclotropia, one finds a visible cycloversion toward the side that is contralateral to the hypertropic eye). This is most commonly found in patients with a history of brain stem stroke.

Cavernous Sinus Syndrome

The ocular motor nerves, the trigeminal nerve, and the sympathetic supply to the eye traverse the cavernous sinus in close company with one another (■ Fig. 10.11). Combined disorders of these nerves are consequently more likely to be caused by intra- or parasellar space-occupying or inflammatory diseases.

Clinical Presentation

The signs and symptoms depend on the speed at which the pathological process progresses. Abrupt expansion of the intrasellar contents, after infarction or hemorrhage into a pituitary adenoma, causes a rapid onset of combined, often bilateral cranial neuropathies, associated with severe headache and uni- or bilateral, often profound, loss of vision. With a subarachnoid hemorrhage, the patient's condition can rapidly deteriorate to the level of a coma. Neuroradiological imaging will show an enlarged sella with intrasellar bleeding and/or necrosis.

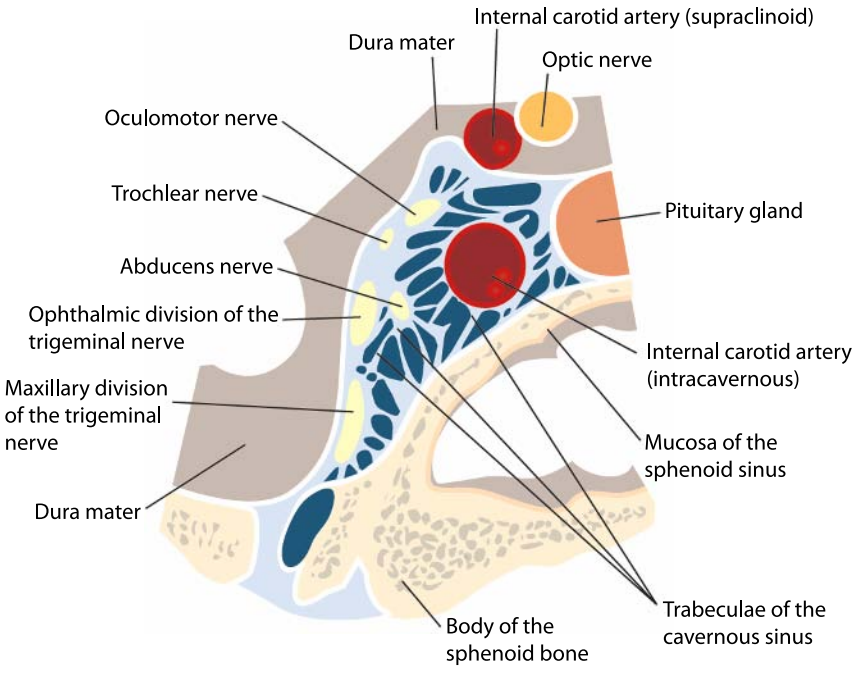


Fig. 10.11. Coronal section through the left cavernous sinus. Within this 2-cm long venous sinus to each side of the sphenoid sinus are the courses of all three ocular motor nerves, the internal carotid artery with its surrounding sympathetic plexus, and the first and second branches of the trigeminal nerve. The supraclinoid carotid barely makes contact with the optic nerve. All inflammatory or mass lesions within the cavernous sinus or in neighboring structures (pituitary gland, petrous apex, nasopharynx) cause both sensory and motor deficits, due to the closely crowded positions of these structures. For combined deficits (e.g., third and sixth nerve pareses) the cavernous sinus is the probable location of the lesion. (Redrawn after: Sobotta, J., Becher, H.: Atlas der Anatomie des Menschen, Chap. 3, Fig. 238. Urban & Schwarzenberg, München, Berlin 1962)

Another acute presentation of combined oculomotor pareses can (infrequently) be caused by rupture of an intracavernous carotid aneurysm. This invariably results in a pulsating proptosis with an arteriovenous fistula that has a very high volumetric flow rate. The changes in the eye's motility are consequently at least partially caused by changes in the mechanical properties of the orbital tissues.

The signs and symptoms of a traumatic fistula following injury to the internal carotid artery within the cavernous sinus will slowly progress for a period of several weeks, ending in a severe, pulsating exophthalmos that threatens to destroy vision, usually (but not always) on the ipsilateral side. In addition to the ocular signs of a direct, high-flow arteriovenous fistula, there is also a major threat of cerebral ischemia, a steal phenomenon caused by short-circuiting of arterial blood into the venous sinuses.

Pearl

The ophthalmologist more often encounters cases of chronic fistulas that produce low rates of volumetric flow. Such patients complain of slowly increasing diplopia, sometimes with pain or hypesthesia in the region innervated by the two upper branches of the fifth nerve (painful diplopia). Examination usually finds and abducens paresis and/or a partial third nerve palsy, less commonly a trochlear nerve paresis.

Primary aberrant regeneration of the third nerve is not common, but is characteristic of a chronic cavernous sinus syndrome. The pupil is initially spared, but a parasympathetic or sympathetic paresis (or a combination of the two) may eventually develop. Pain and hypo- or dysesthesia frequently affect the maxillary branches of the trigeminal nerve more than they do the ophthalmic branches. Optic nerve or chiasmal lesions are uncommon among patients with chronic cavernous sinus syndromes. On the other hand, slowly enlarging pituitary tumors frequently cause visual field defects, but do not commonly affect the extraocular muscles.

Common Causes of Cavernous Sinus Syndrome

Tumors

Nasopharyngeal carcinomas, which have a predilection for men over 60, are the most common tumors to cause cavernous sinus syndrome, and frequently present with symptoms referable to the nasal passages and middle ears. In addition meningiomas, craniopharyngiomas, and metastases are known causes of the syndrome. Most commonly, the abducens nerve and the second division of the trigeminal nerve are affected.

Carotid–Cavernous Fistula

Definition

The direct or traumatic **carotid–cavernous fistula** is a direct communication between the intracavernous carotid and the cavernous sinus. Such fistulas result mostly from trauma and are more frequent than the dural cavernous or spontaneous carotid–cavernous fistulas. These arise spontaneously by formation of a communi-

cation between the dural branches of the internal or external carotid artery and the cavernous sinus.

Dural Carotid–Cavernous Fistula

Dural carotid–cavernous fistulas arise spontaneously and primarily in elderly women. Dural branches of the internal or external carotid are equally involved, and fistulas often arise spontaneously from both sources. The resulting venous congestion causes an ectasia of the orbital and conjunctival veins that are clearly differentiable from inflammatory hyperemia (large, rope-like conjunctival vessels that contrast with white scleral tissue), as well as chemosis with lid swelling, exophthalmos, retinal vascular dilatation with intraretinal hemorrhages, and elevated intraocular pressure. The latter feature is caused by the marked elevation in episcleral venous pressure that is transmitted directly to the anterior chamber. The elevated pressure in the cavernous sinus causes damage to the third, fourth, and sixth cranial nerves, resulting in diplopia. Frequently, patients hear a pulse-synchronous bruit when background noise is diminished, usually when retiring for the evening, and often apparent with particular head positions, such as sleeping on one side. The elevated venous pressure raises a hurdle for the drainage of aqueous humor, which must pass through the trabecular meshwork and into the episcleral veins. This causes a severe form of secondary glaucoma that is very difficult to manage. During applanation tonometric measures of the intraocular pressure, the examiner can easily appreciate the strong, pulsating variation in the size of the circle flattened on the corneal surface. In some cases, both eyes are affected by the fistula. CT or MRI scanning will show expansion in the size of the cavernous sinus, the ophthalmic veins, and the extraocular muscles. The exact diagnosis requires cerebral angiography to show the location of the communication. When loss of vision is threatened, a surgical closure of the fistula can be accomplished by transluminal, selective catheterization and embolization of the fistula. This procedure requires the services of an interventional neuroradiologist.

Direct Carotid–Cavernous Fistula

Direct fistulas are marked by finding of an angiographically demonstrable direct communication between the cavernous sinus and the internal carotid artery. This is most commonly a consequence of severe trauma. The signs and symptoms discusses above are markedly amplified in this type of fistula due to greater volumetric blood flow and higher elevations of orbital venous pressure. The motility deficit is aggravated by the marked distention of the extraocular muscles. Severe pain and a pulse-synchronous bruit ("pile driver noise") are commonly present. Complications include ischemic optic neuropathy, cerebral ischemia, and subarachnoid and/or intracerebral hemorrhages. Management often requires emergent intervention with balloon closure of the large fistulous opening. Ideally, this can be done while also preserving the function of the affected carotid artery, sometimes using coils or detachable balloons for embolization.

Intracavernous Carotid Aneurysm

An intracavernous aneurysm is extra dural, enlarges slowly, and constitutes an enlarging intracavernous mass, much like that of neoplastic, space-occupying lesions. Ruptures are not usual, but when they do open, a direct fistula is formed (see above). Slow growth and frequent thrombosis, in contrast to supraclinoid aneurysms, have a generally good prognosis.

Characteristic signs and symptoms include sixth nerve palsy, frequently with Horner's syndrome, facial pain (first division of the fifth nerve), and sometimes with episodic frontotemporal headache. With large increases in size, there can be involvement of the third and fourth nerves, and even compression of the optic nerve. Confirmation of the diagnosis is provided by CT/MRI scanning, followed by appropriate angiography. For loss of vision with progressive damage to ocular movements and pain, an endovascular approach is indicated. If the aneurysm is well defined and saccular, it can sometimes be closed by coil embolization. In the case of an arteriosclerotic, fusiform aneurysm, permanent closure of the affected artery should be preceded by temporary balloon closure, to test the safety of the approach.

Tolosa-Hunt Syndrome

This disease is caused by a nonspecific, granulomatous inflammation in the cavernous sinus (similar to idiopathic orbital pseudotumor), leading to variable combinations of extraocular muscle pareses on one side with strong, chronic, periorbital pain. The pupil is frequently spared. The syndrome is not common, and the diagnosis can be made only after neuroradiologic exclusion of other types of painful ophthalmoplegia. Spontaneous remission within a few days, relapses (including contralateral involvement) can happen months or years later. If fungal infections have been ruled out (beware of mucormycosis), management is with high doses of oral prednisone (e.g., 5 days of 100 mg/day of prednisone, followed by a tapering of the dose over a 3- to 4-week period. Rapid relief of the symptoms follows within 24 h of the start of treatment.

Pearl

A quick response to corticosteroid therapy is to be expected in cases of Tolosa-Hunt syndrome, but this does not rule out other possible causes of the problem.

Conclusion

For correct diagnosis of infranuclear ocular motility disorders the ophthalmologist must search every site and kind of potential cause. The ophthalmic workup can define the movement deficit, but the affected structures are not visible. So an abduction deficit is not caused by an abducens palsy in every case. It could arise from an orbitomachanical, myogenic, synaptogenic, or neurogenic disease. Only proper characterization of the movement disorder and exclusion of its known mimics will allow a correct diagnosis.

Further Reading

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Chapter 11

Supranuclear Disorders of Ocular Motility

G. Kommerell

There are several different types of eye movements coordinated with one another and regulated by an integrated control system. Refixation saccadic movements serve to redirect the eye, to bring images of interest to the center of the retina. Pursuit movements and optokinetic nystagmus prevent or reduce slippage of the image over the retina. The vestibulo-ocular reflex acts to stabilize the eye's position during head movements. Convergence and divergence movements allow objects at various distances to be imaged on the retinas at corresponding locations. The various types of movement are classified in ■ Fig. 11.1. Supranuclear structures that act through the motor nuclei of the third, fourth, and sixth cranial nerves have the task of coordinating the movements of both eyes, on the one hand, and on the other hand, they must generate the encoded innervational signal patterns for each of the various types of eye movement. The innervational signals are integrated within the cells of the motor nuclei. Consequently, infranuclear (peripheral) lesions compromise the final common pathway – all the eye movement types summarized in ■ Fig. 11.1 – whereas supranuclear lesions can cause separate impairments of individual types of eye movement.

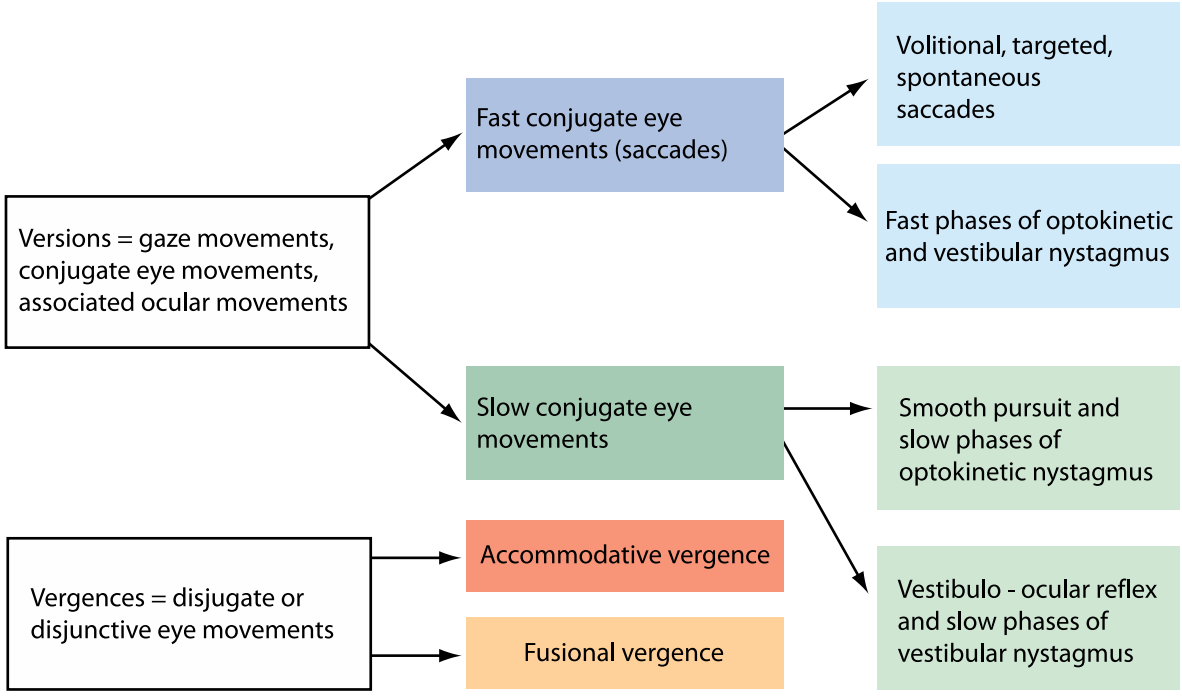

Fig. 11.1. Classification of eye movements

Differential Diagnosis of Supranuclear Disorders of Ocular Motility

The portrayal of supranuclear disorders of ocular motility in this chapter is intended to be a systematic introduction. A patient who shows signs of an eye movement disorder, however, confronts the physician in an entirely different way. For diagnosis, the first step is to determine the location of the lesion. The second step is concerned with identifying the type of lesion. To accomplish this purpose, the following discussion summarizes the most important rules by which supranuclear disorders can be differentiated from other types of disordered eye movement.

For the diagnosis of neuro-ophthalmic disorders the computed tomography (CT) and, more importantly, magnetic resonance imaging (MRI) scans have become indispensable tools. In many cases, these imaging procedures will immediately reveal the location and the nature of the disease process. CT and MRI scans, however, do not release the physician from his/her obligation to classify disorders according to their clinical presentations and to judge whether an imaging procedure is necessary. The neuroradiologist must determine the anatomic region within which high-resolution instruments should be used. Only through precise clinical inquiry can the potential advantages of the CT and MRI be fully realized. In ■ Fig. 11.2, rules are summarized by which eye movement disorders can be attributed to problems in one of the following four regions (oval fields): (1) ocular muscles; (2) orbit; (3) the subarachnoid or cavernous sinus segments of cranial nerves III, IV, and VI, and (4) the brainstem or posterior cranial fossa. The topical classification of eye movement disorders leads the examiner to corresponding groups of differential diagnoses (rectangular fields). Myasthenia (a great mimic) can produce all forms of eye movement disturbances, but will not affect the pupil, damage the optic nerve, or cause changes in the soft tissues of the orbit.

To be able to follow the decision process outlined in the flow diagram, note that four types of eye movements have to be tested:

1. Fast eye movements (volitional refixation saccades)
2. Pursuit movements (and/or optokinetic nystagmus [OKN])
3. Vestibulo-ocular reflex (VOR)
4. Near convergence

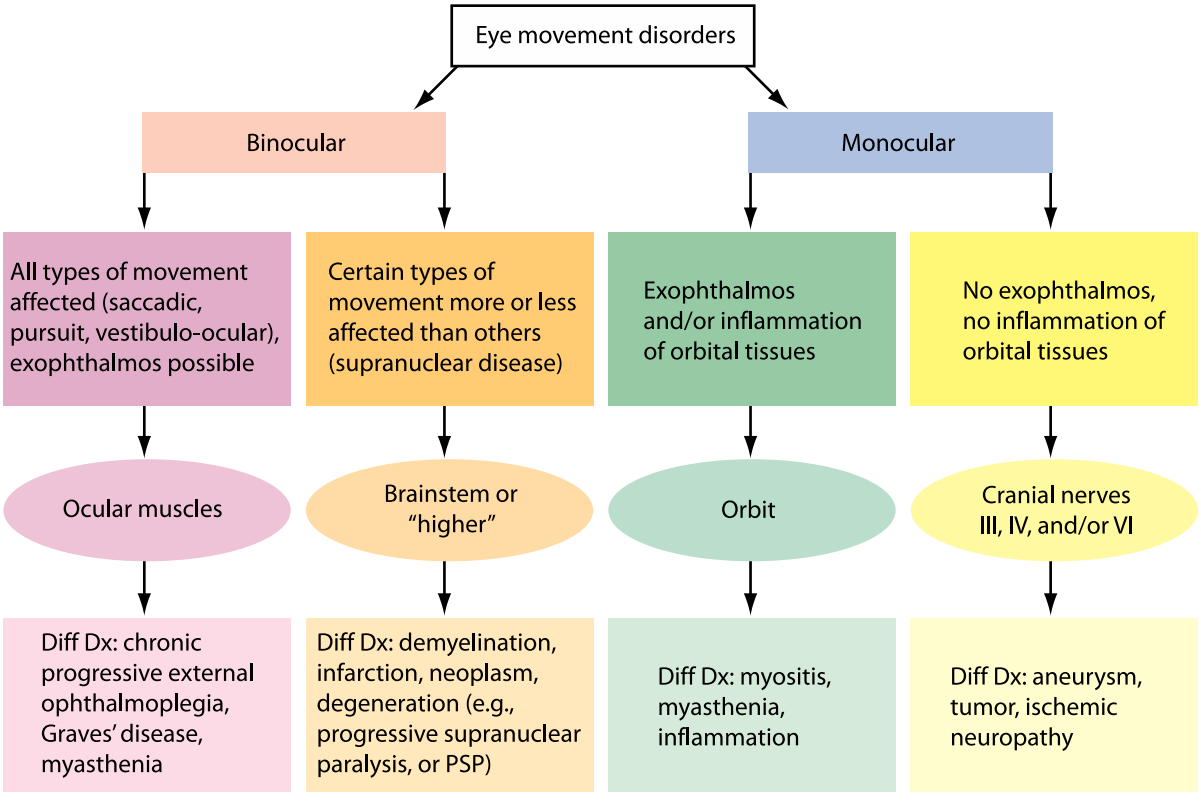

Fig. 11.2. Flow diagram. From symptom to site to cause: a guide to the diagnosis of eye movement disorders.

Fast Eye Movements and Gaze Paralysis

Fast Eye Movements (Saccades)

Definition

At the onset of a **saccade**, the agonist muscle receives an innervational pulse. At the same time, the innervational flow to the antagonist muscle is completely inhibited. The pulse serves to overcome the viscous resistance in the orbital tissues and the inertial mass of the globe to initiate a high-speed rotational movement of the eye. To stop the eye at its intended target, the pulse is followed by an innervational plateau that is higher for the agonist and lower for the antagonist than at the starting position of the saccade. This change of the innervational plateau is referred to as a step.

Saccades appear (1) as volitional refixation movements (changing objects of regard), as (2) involuntary gaze movements without a specific target, and (3) spontaneously. In addition, they participate in optokinetic and vestibular nystagmus as recovery movements (fast phases).

Examination of Fast Eye Movements

Saccadic function is best tested as volitional refixation movements: The patient is asked to change gaze back and forth between one object and another (■ Fig. 11.3). The fixation objects should be presented at an angular separation of about 20 to 30°. Larger angles often require more than one saccade (a normal property of a healthy visual system). Generally, it is sufficient to test refixation saccades between fixed points arranged symmetrically to either side of the midposition, one of them 15° to the right and the other 15° to the left. Similarly, vertical saccades should be tested between points 15° above and below the midposition.

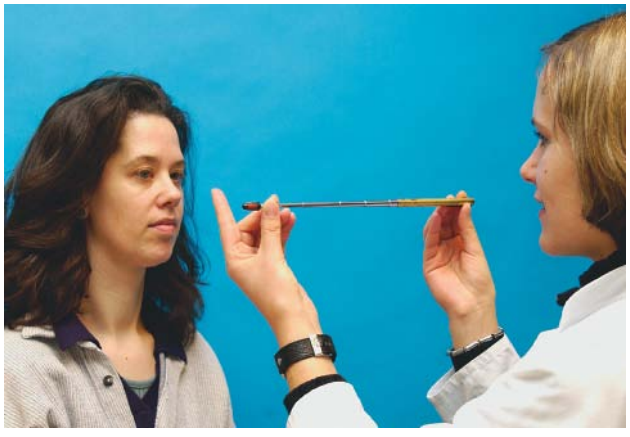

Fig. 11.3. Testing goal-directed saccades for velocity and accuracy. A small rod or pointer with a 30-cm length is held by the examiner in a horizontal orientation and centered at about a 50 cm distance from the eyes. The examiner asks the patient to change fixation from one end to the other and back again, using the forefingers to signal the moments of alternation at about every 2 s

Pearl

When examining saccades it is just as important to notice their velocity as it is their accuracy.

Gaze Palsy

Definition

A **gaze palsy** appears as a limitation of conjugate movement in both eyes, arises from damage to cerebral structures, and can be an isolated deficit for binocular movements to the right, left, up, or down.

A pure gaze paralysis affects both eyes equally, and there is no strabismus, unless an unrelated disorder antedated onset of the paresis. Such pure findings are not common, however. Due to the proximity of the supranuclear structures to the nuclei and fascicles of cranial nerves III, IV and VI, gaze palsies are frequently found in association with paretic strabismus.

Psychogenic Inhibition of Gaze Movements

Prior to initiating a diagnostic workup for a gaze palsy, one should consider whether the problem might be psychological in origin. With such a problem the patient cannot, for instance, be coaxed into changing gaze direction past the midline to one side. Otherwise, however, ocular motor functions will be normal. In particular volitional saccades from the "good" side to the midposition will appear normal.

Pontine Gaze Palsy

The lesion causing a pontine gaze palsy lies ipsilateral to the paretic gaze direction, and is located either in the abducens nucleus or in the paramedian pontine reticular formation ([PPRF] ■ Fig. 11.4). Lesions of the abducens nucleus affect both the motoneurons of the abducens nerve and the internuclear neurons that project to the motoneurons of the contralateral medial rectus (■ Fig. 11.5). The saccadic movements of both eyes toward the side of the lesion are impaired.

With total loss of the structures within the PPRF, all fast movements of both eyes to the ipsilateral side will be lost. Pursuit movements, on the other hand, and movements of the VOR are retained. When damage to the PPRF is incomplete, saccadic movements to the ipsilateral side can be elicited, but their speed is reduced.

Eye Movement Disorders Caused by Damage in the Cerebral Hemispheres

Focal lesions to individual areas of cerebral cortex do not cause a gaze palsy. Rather, there are discrete deficits that require complex experimental testing procedures for their detection. Therefore, for example, patients with a defect in the entire frontal eye field can certainly generate gaze movements to the contralateral side. However, when given the task of looking toward the opposite of an object, the patient will be unable to suppress the reflex that draws his/her eyes to the object.

Pearl

Strokes with damage to the internal capsule more often will produce gaze palsies, since this structure contains a close bundling together of descending fibers from many areas of the cortex. This allows most or all of the efferent fibers to be simultaneously damaged. Gaze to the opposite size will be paralyzed, and there will be a tonic perseveration of gaze direction ipsilateral to the lesion: the patient is said to be looking at his/her own lesion.

In contrast to the pontine type of gaze palsy, hemispheric palsies of gaze generally disappear within 1 or 2 weeks. Patients admitted to hospital with cerebral strokes will have such findings for only a brief period following admission.

Vertical Gaze Palsy (Dorsal Midbrain Syndrome: Parinaud's Syndrome)

The supranuclear structures responsible for control of vertical eye movements are clustered around the Sylvian aqueduct, rostral to the quadrigeminal plate. Important structural elements include:

1. The rostral interstitial nucleus of the medial longitudinal fasciculus ([riMLF] ■ Fig. 11.4), which generates the pulse for the fast eye movements in vertical directions (analogous to the function of the PPRF for horizontal movements)
2. The nucleus of Cajal, which lies close by, just below the riMLF; it integrates the pulse to form the step component of the pulse/step signal pattern for saccadic movement in vertical directions, allowing for stabilization of gaze direction at the completion of the saccade (analogous to the function of the nucleus prepositus hypoglossi (NPH) for horizontal movements)
3. In the posterior commissure are the decussating fibers from the riMLF and the nucleus of Cajal that project to the third and fourth cranial nerve nuclei (■ Fig. 11.5 b).

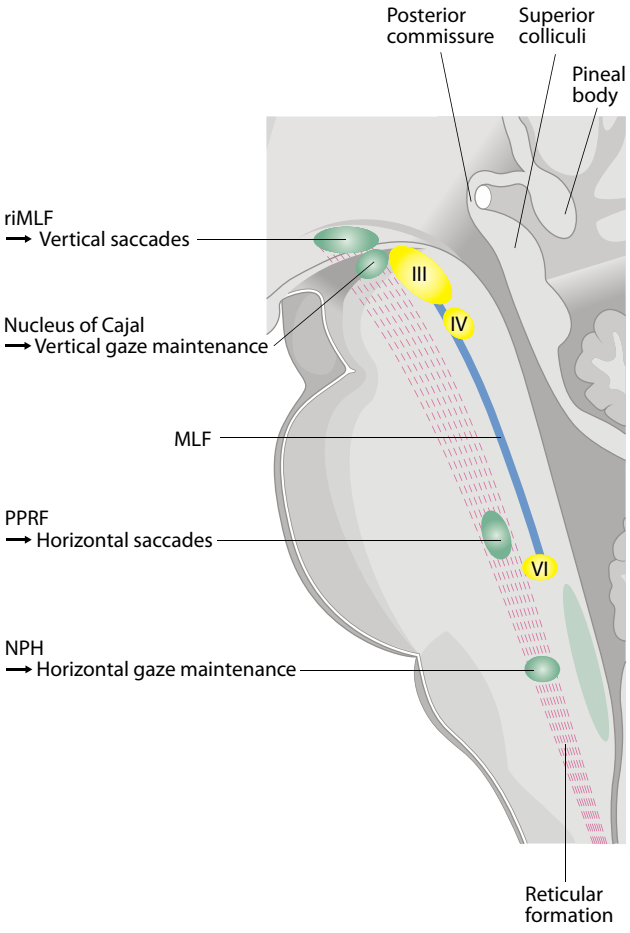

Fig. 11.4. Supranuclear and nuclear structures of the ocular motor system. View from the left-hand side of the translucent brainstem. The paramedian pontine reticular formation (*PRRF*) controls horizontal saccades, and the rostral interstitial nucleus of the medial longitudinal fasciculus (*riMLF*) controls vertical saccades. The PPRF projects its pulse for horizontal saccades directly to the ocular motor nuclei on one hand, and on the other to the nucleus prepositus hypoglossi (*NPH*). Here the signal is integrated to produce a step, which is also sent to the motor nuclei. The arrival of the pulse at the extraocular muscles generates a ballistic movement of the eye to the new position, which is then stabilized at its new position by the step signal. *III* = oculomotor nucleus. *IV* = trochlear nucleus, *VI* = abducens nucleus

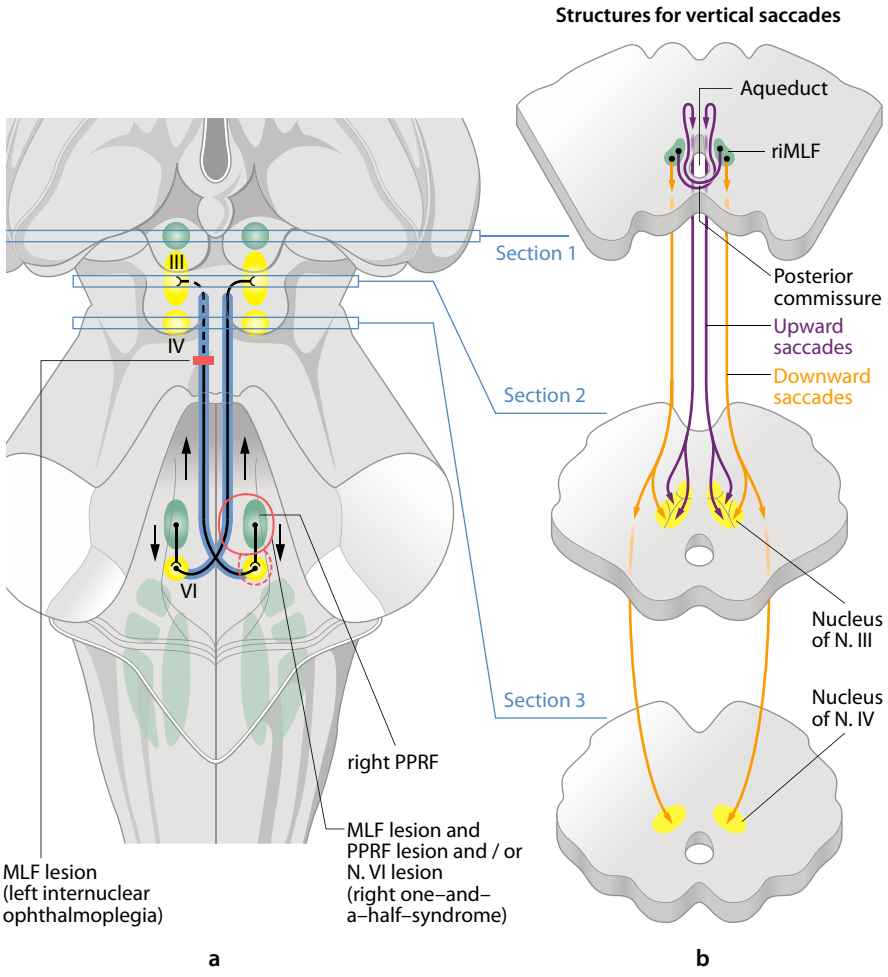

Fig. 11.5. a,b Supranuclear and nuclear structures of the ocular motor system. View of the translucent brainstem from behind. The impulse for right gaze is generated in the right PPRF. The signal is transmitted to the right abducens nucleus (*VI*). There, in addition to activating the neurons of the abducens nerve, the impulse also activates internuclear neurons whose axons decussate and project through the left medial longitudinal fasciculus (*MLF*) to the nuclear complex of the oculomotor nerve. The *MLF* passes the signal on to the subnucleus of the left medial rectus. A lesion of the left *MLF* causes the adduction signal meant for the left medial rectus to fall short of its goal. The result: The left eye is unable to adduct as part of a gaze shift to the right side. Other inputs to the left medial rectus subnucleus remain functional, allowing the muscle to contract when participating in an accommodative or fusional convergence movement. The convergence signal arises in the midbrain, and does not travel through the *MLF*. A right one-and-a-half-syndrome is caused by a lesion of the right *PPRF* (both eyes cannot saccade to the right) plus a lesion of the right *MLF* (the right eye cannot saccade to the left)

Lesions caused by pineal tumors, for example, can affect all three of these supranuclear structures where they are grouped around the rostral segment of the aqueduct. This commonly elicits dorsal midbrain syndrome, also known as Parinaud's syndrome. If only upgaze movements are affected, fibers that decussate disconnect in the posterior commissure of the midbrain. Isolated downgaze palsy is rare. It is nearly exclusively due to an occlusion of the posterior thalamo-subthalamic artery, which penetrates the brainstem from its anterior surface.

Pearl

In association with Parinaud's syndrome, convergence–retraction nystagmus frequently develops when the patient attempts to look upward. This phenomenon can be amplified by using an optokinetic stimulus moving downward, thereby eliciting a nystagmus with its fast phase in the upward direction. This in turn elicits a train of converging and retracting movements of both eyes. The locus of damage causing this phenomenon does not appear to be focal, since many disease processes in the pretectal midbrain can be found associated with convergence retraction nystagmus.

Parinaud's syndrome is often combined with a loss of the pupillary light reaction and retention of accommodative miosis (so-called pupillary light/near dissociation; see Chap. 5).

Video 11.1

Oculomotor Apraxia

Definition

Oculomotor apraxia describes an eye movement disorder characterized by loss of or severely diminished volitional saccades with retention of the fast phases of vestibular nystagmus. Reflexive saccades stimulated by objects of interest in the peripheral visual field may be disordered or normal.

Congenital oculomotor apraxia (Cogan's syndrome) manifests in newborn infants. During the first 3 months of life, affected infants are unable to look toward objects held out to them, and may be mistakenly thought of as blind. In the following months of development, instead of normal changes in gaze position, a compensating strategy evolves. Thrusting movements of the head in the direction of interest are used to bring the eyes into alignment with the object of interest. Since VOR movements largely negate the movement of the eyes with head turn, the child must turn the head well beyond the point of interest, allowing the limits of duction movements to finally position the eyes as desired. In the second phase, with the eyes having taken up fixation, visual pursuit and VOR inputs serve to keep the eye fixed on the object, while the head is then able to return to the midposition. Congenital oculomotor apraxia gradually disappears during the first two decades of life. In adulthood, many of these patients require only a small head movement to serve as a "trigger" that initiates a refixation saccade.

Pearl

Congenital oculomotor apraxia affects only horizontal eye movements. Rare acquired forms of oculomotor apraxia develop in the setting of severe cerebral disease, and these cases have impairment of both horizontal and vertical saccadic movements.

It is not known where the damage responsible for oculomotor apraxia is located. The PPRF can be excluded as the site of the lesion, since vestibular stimuli elicit fast phases of nystagmus in such patients.

Gaze-Evoked Nystagmus

Definition

Gaze-evoked nystagmus is the result of a gaze-holding deficit. The eyes can indeed be moved into an eccentric position by saccades or by the VOR. However, they cannot be held in the eccentric position. Instead, they drift back toward the midline and must be redirected repeatedly toward the object of regard. This gaze-evoked nystagmus can be so pronounced that the eyes return all the way to the midline during the slow phase of the nystagmus. The drift is at first quick but then slows gradually as the eyes approach the midline.

The structures responsible for fixation maintenance are widely dispersed in the brainstem (particularly in the nucleus prepositus hypoglossi) and in the cerebellum. Thus, gaze-evoked nystagmus tells the examiner very little about the location of a lesion.

Note

Gaze-evoked nystagmus should cause the physician to ask whether tranquilizer or antiseizure medications are being used. Only when drug effects have been ruled out should the workup proceed in a search for disease in the cerebellum and/or brainstem.

Endpoint nystagmus refers to a minor gaze-holding deficit that should not be regarded as clinically important. Endpoint nystagmus appears only beyond a gaze eccentricity of about 35°.

Saccadic Dysmetria

Definition

Refixation saccades are considered **dysmetric** when they consistently over- or undershoot their intended target. This leads to small corrective saccades before the target is properly centered in the visual field. Saccades that fall short of the mark are said to by hypometric, while those that move past the target and then double back are hypermetric.

Testing for dysmetria is best done with the method illustrated in ■ Fig. 11.3.

Hypometric saccades are not necessarily pathological; they can be the product of inattention or poor cooperation. Hypermetric saccades on the contrary are always pathological and strongly suggest the presence of a lesion in the cerebellar vermis.

Dysmetria caused by Wallenberg syndrome (infarction of the lateral medulla) on the left side will produce the following findings: saccadic movements to the left are hypermetric, whereas those to the right are hypometric. Upward saccades veer to the left, and downward saccades veer to the left. This so-called saccadic lateropulsion can be understood as the result of an ipsilesional impulse added to each saccade (■ Fig. 11.6).

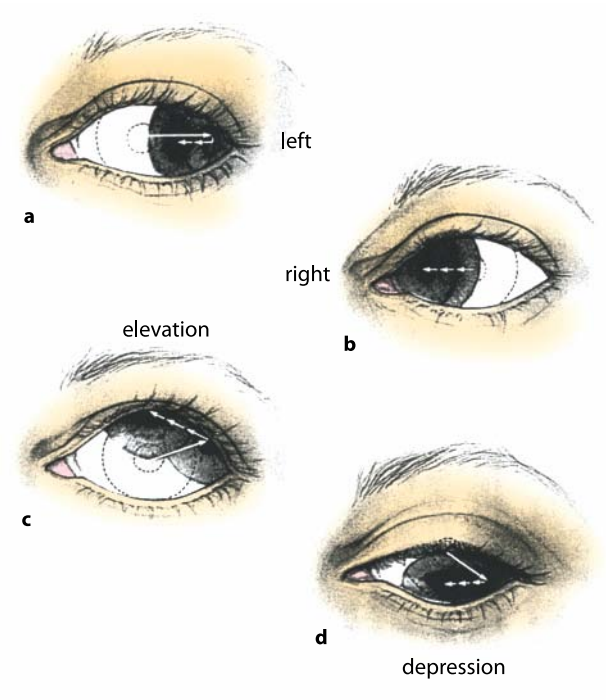

Fig. 11.6. Saccadic lateropulsion to the left following a left side infarct of the lateral medulla (Wallenberg syndrome). The intended target of the movement is reached only with the help of several corrective, hypometric saccades. **a** Hypermetria to the left with corrective hypometric saccades to the right. **b** Hypometria to the right. **c** Leftward diversion (lateropulsion) of upward saccade followed by hypometric corrective saccades up and to the right. **d** Leftward diversion of downward saccade followed by hypometric corrective saccades down and to the right

Internuclear Ophthalmoplegia and the One-and-a-Half Syndrome

Internuclear ophthalmoplegia is caused by damage to the internuclear neurons that exit from the abducens nucleus, decussate to the contralateral side, rise in the medial longitudinal fasciculus (MLF), and terminate in the subnucleus of the medial rectus in the nuclear complex of the third cranial nerve (■ Fig. 11.5).

Definition

An **internuclear ophthalmoplegia (INO)** is present if an eye cannot be adducted when changing gaze direction, but will adduct during accommodative convergence (■ Fig. 11.7).

To detect this diagnostically important superiority of adduction during accommodative convergence, even in subtle lesions of the MLF, the following procedure is advisable. At first, the involved eye is stimulated to adduct as far as possible via a conjugated version by letting the patient follow a distant target to the relevant side. Subsequently the examiner determines whether the addition of accommodative convergence allows the eye to adduct any further, by bringing the target near to the patient, keeping it on the relevant side. Even slightly diminished adducting capacity becomes apparent on saccade testing: The speed of adduction in one eye will be visibly less than the abducting velocity in the other eye. For wide-angle saccadic movements, the examiner can see that the lateral rectus wins the race to one side, while the adducting fellow eye has to catch up. This is true for both unilateral and bilateral INO.

In addition to accommodative convergence, fusional vergence can be retained, so that the patient shows no manifest strabismus. Exodeviations develop in patients with pronounced INO and weak fusional convergence. If an antecedent exophoria was present before the damage to the MLF occurred, disruption of binocular cooperation by the INO will then allow the exodeviation to be fully expressed. In extreme cases of total loss of function in the MLF on both sides (usually the result of a midline demyelinating plaque), the eyes may adopt a bilaterally exodeviated position, which has been dubbed the wall-eyed bilateral INO, or WEBINO syndrome.

In addition to an INO, midbrain disease can also cause a paresis of accommodative convergence. In this case, the INO cannot be proven, but can be suspected when the paresis is limited to the medial rectus and all other muscles innervated by the third nerve have retained their function.

Pearl

Often an INO will be accompanied by a gaze-evoked nystagmus. The basis for this is that structures responsible for the maintenance of eccentric gaze positions are located near the MLF. The nystagmus is said to be dissociated, since the velocity of the adducting eye has been slowed, but the movement of the abducting eye is undiminished. (When speaking of a dissociated nystagmus, one means that the nystagmus is not the same in both eyes.)

Occasionally, in addition to the damage of one MLF, the neighboring PPRF and or the adjacent abducens nucleus on the ipsilateral side are simultaneously damaged (■ Fig. 11.5). This produces the so-called one-and-a-half syndrome.

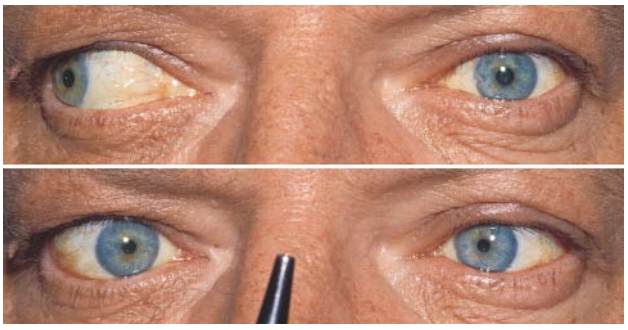

Fig. 11.7. Left-sided internuclear ophthalmoplegia (INO). The left eye cannot participate in a gaze shift to the right, but is able to adduct during accommodative convergence movements. (This figure is a courtesy of Prof. V. Herzau)

Definition

One-and-a-half syndrome is present when the horizontal movement of one eye has been completely lost, and it can neither adduct nor abduct (the "one"), while the fellow eye has lost its capacity to adduct, but retains normal abduction movements (the "half").

Damage to the right PPRF (and/or the right abducens nucleus) causes a paralysis of abduction in the right eye and of adduction in the left eye, an ipsilateral, horizontal gaze palsy. Simultaneous damage to the right MLF produces a paralysis of adduction of the right eye, while the capacity for abduction of the left eye is retained. Thus, one-and-a-half syndrome is caused by disease located on the side ipsilateral to the eye with total loss of horizontal movement.

Several disorders can cause an INO. A particularly frequent pattern is the subacute onset of an INO in a patient with multiple sclerosis. Its onset and recovery have the same timing as that in retrobulbar optic neuritis: The paralysis begins more or less abruptly, and subsequently improves in a course lasting weeks or months.

Pearl

The INO of multiple sclerosis is frequently bilateral and is found primarily in younger patients. Unilateral INO occurs more frequently in the elderly or in patients with systemic vascular disease. The mechanism is an infarction in the distribution of a small paramedian artery that supplies the region containing the MLF, i.e., at the levels from the sixth nerve nucleus caudally to the third nerve nuclear complex rostrally. Vessels in this region tend to respect the sagittal plane, supplying areas that do not cross the midline. Such lesions are very small and difficult to detect on MRI scanning.

Video 11.2

Like all other movement disorders, the INO can be persuasively mimicked by ocular myasthenia. If the adduction deficit is variable, an edrophonium test can reveal a myasthenic cause (see Chap. 10).

Ocular Tilt Reaction

In the petrous pyramid of the temporal bone, where the labyrinthine canals converge, are two bony recesses, the utriculus and the sacculus. They contain ciliated sensory receptors. Adherent to the ciliae are tiny lime concrements called otoliths. Gravitational pull on the otoliths bends the ciliae downward, generating a neural signal that defines the static rotational orientation of the head. Depending on the direction of head tilt, the sensory receptors are stimulated or inhibited, allowing the otolithic apparatus to provide the brain with an answer to the question: Which way is up? The otolithic apparatus thus functions as an accelerometer and tilt receptor that measures both the force of gravity and the static orientation of the head – a graviceptive sensory organ. As an integral component of the vestibular system, the otolithic apparatus feeds data to the brain through the eighth cranial nerve (■ Fig. 11.8).

Definition

A unilateral interruption of the otolithic afferent pathway causes the **ocular tilt reaction (OTR), which has four components:**

1. A yoked rotational displacement of both eyes around the visual axis
2. A vertical strabismus (skew deviation)
3. A head tilt to one side
4. A tilt of the subjective visual perception of the vertical

All four components are tilted in the same direction. (In the example diagrammed in ■ Fig. 11.8, the tilt is to the right.)

The rotational displacement of both eyes and the skew deviation are caused by an interruption of the otolithic signal to the superior rectus of the ipsilateral eye and the inferior oblique of the contralateral eye (■ Fig. 11.8). The head tilt arises from a defective projection to the neck muscles and the tilt of the subjective visual vertical is caused by a faulty projection to the vestibular cortex. The cyclodeviation and the tilt of the subjective visual vertical are in the same direction in both eyes, but their magnitudes can differ. A lesion of the otolithic pathway in the caudal brainstem (medulla oblongata or caudal pons) will cause a tilt to

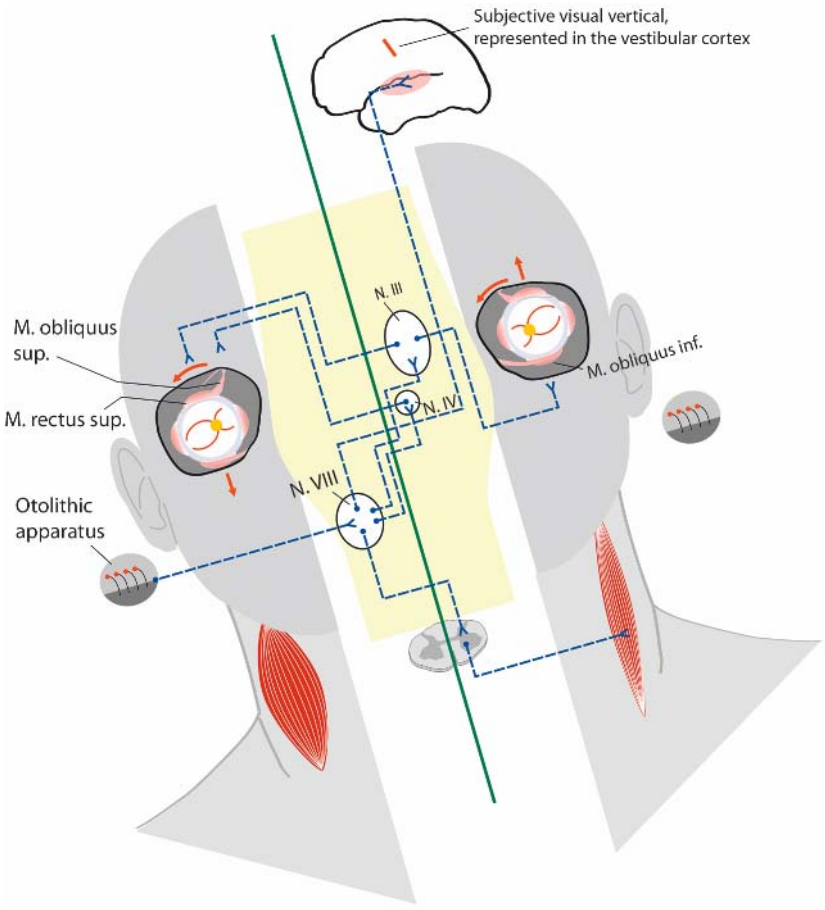

Fig. 11.8. Graviceptive pathway. With a lesion of the pathway that carries the input signal from the right otolithic apparatus to the ocular motor nuclei, an "ocular tilt reaction" (OTR) to the right is produced

the ipsilateral side, whereas a lesion damaging the same path in the more rostral portions of the brainstem (rostral pons or midbrain) will cause a tilt to the opposite side. This reversal of direction at the mid pons is due to a decussation of the otolithic pathways in the pons (■ Fig. 11.8).

The rotational displacement of both eyes around their visual axes can be seen in the rotational orientation of the line between the optic disc and the fovea. Fundus photography is the preferred medium for documentation. Alternatively, the position of the physiologic blind spot relative to the horizontal meridian can be plotted with kinetic perimetry. Ordinarily, the center of the optic disc lies about 2° above, and the center of the blind spot lies 2° below the horizontal meridian. This corresponds to a rotation of about 7°. The subjective visual vertical (and the subjective horizontal, i.e., the entire image) appears tilted in the same direction, as is the cyclodeviation of the eyes around their visual axes, though not always to the same extent. The subjective visual vertical should be determined by letting the patient adjust a narrow streak of light in a darkened room under monocular observation. The rotational orientation of the streak then measures the error in the subjective visual vertical.

Pearl

A simple and original method for the determination of the subjective visual vertical has been designed by Lars Frisén (Göteborg). The patient peers into an open bucket that obscures visual clues to orientation and has a straight diameter line painted through the center. The patient has the task of peering into and rotating the bucket such that the line appears to be vertically oriented. The outside bottom of the bucket has a plumb bob hanging from its center, and the rim is labeled with a graduated scale. Where the plumb line intersects the rim marks the orientation chosen by the patient, providing a direct measure of the (abnormal) subjective visual vertical. This device has not been commercialized, but its design is simple enough that interested users can make their own.

If a patient indicates the subjective vertical tilted to the right (clockwise), he/she will perceive vertical structures (e.g., door frames) as if they are all tilted to the left (counterclockwise). In a natural environment, this faulty perception will be seen for the first few minutes or hours after the lesion's onset, after which there is rapid adaptation with a

return of normal spatial perception. A residual effect of this sort of lesion, however, can often be detected even months after the adaptive recovery by measuring the subjective vertical when only the streak of light is visible, having removed all other clues to orientation.

Pearl

The ocular tilt reaction is the most common sign of intrinsic brainstem damage. It is found in about 20% of all unilateral brainstem lesions. Not always are all four components expressed. The tilt of the subjective visual vertical is the most frequent.

Pursuit Movements and OKN

Pursuit Movements

Definition

Pursuit movements are the motor response of the eye to a continuously moving object of regard. The smoothness of the pursuit movements is of the greatest diagnostic importance. Overtaxing of the smooth pursuit movements results in the generation of saccadic corrective movements (saccadic pursuit).

Testing Pursuit Movements

The examiner uses a fixation object fastened to the end of a rigid wand. This is moved at a slow and constant rate, back and forth, up and down, while the examiner watches the eye movements of the patient. The movement of the test object should cover an amplitude of 10° to either side of the midposition (total motility angle of 20°) for both horizontal and vertical movements. Smooth pursuit movements should be seen for speeds of the target up to about 30°/s. If the test object is moved too quickly, the pursuit mechanism will be overtaxed and will have to introduce a series of small, corrective saccades to keep up with the target, so that its image remains on the fovea. The pursuit movement is said to be saccadic. The capacity of the pursuit mechanism to maintain smooth movements will vary with the patient's age and level of attentiveness. If the patient's pursuit movements become saccadic at speeds of about 15°/s or if the speed is notably different between the two eyes, the pursuit function is defective. If the test object is not presented against a featureless background, but is rather seen before a complex background that has contrasting elements, the maximum speed of smooth pursuit movements will be diminished about 20%.

Optokinetic Nystagmus

Definition

Optokinetic nystagmus is the motor response of the eye to a continuously moving pattern that has contrasting elements. The OKN consists of slow phases that reduce or prevent movement of the image across the retina, and of fast phases that reset the eyes to succeeding elements of the pattern.

An optokinetic stimulus can be generated either by movement of the surrounding environment, or by movement of the observer in a stationary environment. Thus, OKN will be stimulated when the observer directs visual attention onto a passing railroad train, but will also be stimulated in a passenger on the train who is viewing the passing scene through a window.

Testing OKN

Experimental testing of OKN in a research laboratory has traditionally used a rotating drum marked with alternating black and white stripes. For clinical tests of OKN, the examiner uses a patterned ribbon or band of material, held approximately 20 in. away from the eyes. The band is drawn in the direction to be tested, holding it at a stable location with one hand while pulling it past the stabilized location with the other hand (■ Fig. 11.9).

Fig. 11.9. Testing optokinetic nystagmus (OKN). The patient should watch the pattern on the OKN tape. The examiner draws the tape at a steady rate from left to right, and then from right to left in alternating fashion. The analogous method is used to elicit upward and downward OKN movements

Pearl

OKN function is judged, noting whether the speed of the slow phase matches that of the passing stimulus.

Video 11.3

The principal observation to make is a comparison of motor responses to the stimulus movements for both left and right directions. The fast phase of horizontal OKN should be both symmetrical and easily elicited for both the left and right directions of stimulus movements. Differences between upward and downward OKN are not usually pathological. The response to downward movement is normally weaker than it is to upward movement.

Just as in the description of vestibular nystagmus, OKN direction is named (by convention) according to the fast phase. Thus, if the pattern is moving to the patient's left side, the fast phase will be toward the patient's right side.

Note

To avoid confusion of sides when describing OKN, one should avoid descriptions of the fast-phase direction, and should instead describe the direction of stimulus movement relative to the patient's position, for example, "Weak OKN for pattern movement to the left."

Disorders of Pursuit Movements and OKN

An impairment of pursuit movements in most cases is coupled with a deficit for the slow phase of OKN.

A functioning area of the primary visual cortex in one hemisphere is sufficient to generate normal pursuit movements and normal OKN responses to both sides. Thus, if there is a homonymous hemianopia, caused by an isolated lesion in the primary visual cortex, the examiner will find no abnormality of OKN. However, if there is damage to the deep white matter in the parieto-occipital lobes on one side, there will be a loss of pursuit movement and of the slow-phase component of the OKN to the ipsilesional side (see also Chap. 13, ■ Fig. 13.1).

In addition, lesions in the brainstem and the cerebellum can damage both pursuit movements and the slow phases of OKN. When there is a cerebellar lesion, pursuit movements and the slow phases of OKN will be faulty to the ipsilateral side, the same as for a lesion in the deep white matter of the cerebral hemisphere. Conversely, pontine disease will cause pursuit movements and OKN slow phases that are diminished toward the contralateral side.

In the presence of a gaze-evoked nystagmus, pursuit movements will not be testable with the methods just described, since the fast phases of the gaze-evoked nystagmus will inevitably add saccades. In this case one can use an alternative method in which the ability of fixation maintenance to suppress the VOR is determined (■ Fig. 11.10). The patient is seated on a swivel chair and turned to left and/or right while holding out his/her folded hands and fixing on the thumbs. Thus, the target is rotated in synchrony with the patient. Normally the pursuit mechanism is able to suppress the vestibulo-ocular reflex and stabilize the eyes' position so that slippage of the target's image over the retina is prevented. If the pursuit mechanism is faulty, however, a vestibular nystagmus will intrude: During the slow phases, the eyes will veer away from the target, and during the fast phases, they will refixate on the target. This causes the patient's acuity to drop.

Fig. 11.10. Testing the ability to suppress the vestibulo-ocular reflex (VOR). The patient sits on a swivel chair and turns in one direction, and then the other, while fixing on his/her thumbs held out at arm's length. The pursuit system should suppress the vestibular nystagmus that would otherwise be seen

Pearl

If the vestibular nystagmus cannot be suppressed when turning the swivel chair to the right, one can infer that there is a disturbance of pursuit movements to the right.

Vestibulo-Ocular Reflex

Physiologic Basis for the VOR

The VOR arising from the labyrinthine canals of the inner ear serves to stabilize the eye's position when the head is turned, whether side to side or up and down or around the sagittal axis (■ Fig. 11.11). This allows stabilization of the retinal image and prevents blurring. The vestibular system compensates for short and quick changes in rotational

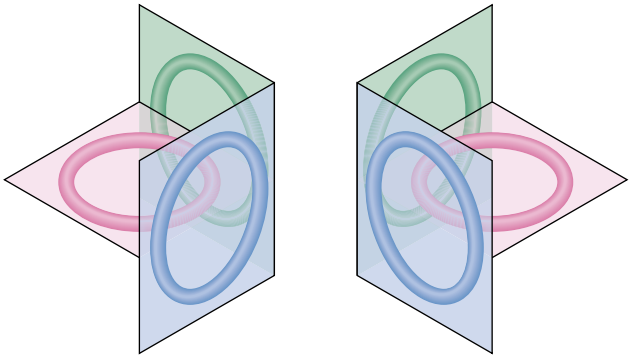

Fig. 11.11. Semicircular canals, arranged in three spatial planes. With changes in rotational speed the fluid endolymph in the canals lags behind the head movement due to inertia. The resulting flow of fluid displaces the cupola receptors, changing their rate of firing. Depending on the direction of rotational acceleration, the resting activity is either increased or inhibited. With the head held stationary, the firing rates of all six canals are in equilibrium. With rotational acceleration to the right, the right horizontal semicircular canal is activated, and the left is inhibited. This reciprocal pattern of innervation produces a compensatory movement of both eyes to the left. Similar reciprocal wiring of the vertical canals in the two other spatial planes control the vertical and the cyclorotational VOR

acceleration of the head, while the optokinetic system compensates for longer and slower head movements. Therefore, for example, the VOR minimizes retinal image displacement during nodding or shaking movements of the head that unavoidably arise during activities like walking or driving a car. OKN would be too slow to achieve this.

Pearl

The dominance of the VOR for image stabilization over the pursuit and OKN systems at high velocities can be demonstrated by one's self: A passage of text will remain readable during rapid rotational movements of the head, whether side to side or up and down, but if the head is held fixed in position and the text is shifted at the same angular velocity as the head in the previous experiment, it will appear blurred.

Tests of the VOR

The patient is asked to read small characters while turning his/her head back and forth with increasing frequency. For examination of the vertical VOR, the patient is asked to read while nodding the head up and down.

There is a threshold frequency beyond which the VOR of a healthy visual system cannot keep up, and illusory movements of the external world intrude. Such illusory movement is called oscillopsia. For a comparative assessment, it is sufficient for the examiner to compare the patient's threshold frequency with his own.

For separate testing of the right and left vestibular apparatus, caloric lavage of the external auditory canals is necessary. This is usually done by an otolaryngologist, since the safety of the procedure depends on a prior confirmation of intact tympanic membranes.

Tests for Nystagmus While Excluding Fixation

The tests are conducted in a dark room. The patient is asked to look straight ahead. The examiner observes the eyes with the aid of a small, handheld flashlight, illuminating the eyes from below. Residual image elements of the room's contents are thereby hidden from the patient by the glare of the light. One can also use Frenzel glasses that have incorporated light sources to accomplish the same purpose: exclusion of fixation. The magnifying lenses of the Frenzel glasses assist the examiner in observing the eye movements.

Another good examination technique is to illuminate the optic disc of one eye with the small spot of a direct ophthalmoscope, while the other eye is occluded. The patient then sees only scattered light, and the examiner can assess the ocular movements and estimate their amplitude and velocity relative to the diameter of the disc (about 7°).

Note

When answering the question of whether a nystagmus is present or not, the slow phases are decisive. However, the name given to the direction of the nystagmus refers to the fast phases. During ophthalmoscopy, the examiner should keep in mind that the nystagmus is not named for the direction of the fast phases seen in the fundus, but rather for the direction of the fast phases of the anterior segment, and are opposite to the direction of the fundus image. Therefore, the ophthalmoscopic view of the fundus in an eye with a down-beating nystagmus will be an up-beating of the retina.

Functional Loss of One Vestibular Organ

Acute loss of the right vestibular organ's function will produce a nystagmus that has quick phases to the left with a rotary component (quick phases toward the side opposite to that of the lesion). This peripheral vestibular nystagmus will be clearly apparent only during concealment of the image features that allow the pursuit and fixation maintenance mechanisms to stabilize the eye. The basis for peripheral vestibular nystagmus is an imbalance of the afferent signals from the right and left vestibular organs: If the right ves-

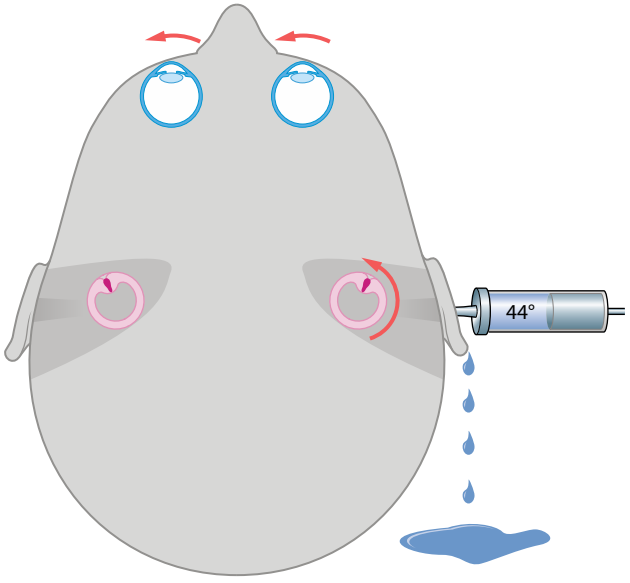

Fig. 11.12. Caloric testing of vestibular function. Fixation is excluded, e.g., by means of Frenzel glasses. With the head reclined, the external auditory canal on one side is irrigated with water at 44°C. This warms the endolymph in the lateral sector of the horizontal canal, whereas the endolymph in the medial sector of the horizontal canal remains unaffected. The warmer fluid in the lateral sector tends to rise, setting up a weak circulation within the canal. This tiny circulation suffices to bend the ciliae on top of the sensory cells of the cupula. With a healthy vestibular apparatus, nystagmus is generated with its slow phases in the same direction as the circulation of the endolymph in the right stimulated canal

tibular organ is damaged, the afferent signal (in case of a stationary head the resting activity) expected to come from both sides comes from the left side only. This disequilibrium is interpreted by the brain to mean that the head is turning to the left. This causes a feeling of dizziness, comparable to the feeling that a healthy observer has when stepping off a carousel. The environment appears to be turning in the direction opposite to that of the slow phase, and a sensation of nausea is often present.

Fortunately, the nystagmus caused by damage to one vestibular organ will be inhibited within a few days by adaptation within the CNS. After adaptation, the diagnosis of a unilateral loss of vestibular function can still be established by caloric testing: Warm-water lavage of the external auditory canal on the diseased side should in a normal case cause slow nystagmus phases to the opposite side. With loss of function, however, no nystagmus is elicited (■ Fig. 11.12).

Functional Loss of Both Vestibular Organs

Bilateral loss of vestibular function is not accompanied by any disequilibrium of the vestibular afferents from both sides, so there will be no nystagmus. However, there will be loss of vestibular reflexes. Consequently, the patient will experience illusory movement of the environment (oscillopsia) during any rotational movement of the head. Therefore, for example, the patient cannot read the station clock when running to catch a train; the patient has to stop moving. Typical causes of bilateral loss of vestibular function include Ménière's disease and chronic use of aminoglycoside antibiotics. In addition, disease within the brainstem, such as multiple sclerosis, can damage the VOR, resulting in oscillopsia.

Central Vestibular Nystagmus

Central vestibular nystagmus is caused by damage to the vestibular nuclei or to their connections with the ocular motor nuclei. Since the vestibular, optokinetic, and pursuit systems all converge on a common final pathway through the vestibular nuclei, they are all impaired. Due to the loss of the optokinetic and pursuit systems, the sufferer is unable to stop the nystagmus-driven movement of images across the retina. Consequently, central vestibular nystagmus (in contradistinction to peripheral vestibular nystagmus) cannot be suppressed by the fixation maintenance system. The result is intractable oscillopsia. Treatment is largely unsatisfactory. Drugs like baclofen and clonazepam when given in sufficiently high doses can dampen the nystagmus, but often produce an unacceptable level of somnolence.

Downbeat Nystagmus

Definition

Downbeat nystagmus is a central vestibular nystagmus whose fast phases are downward.

Downbeat nystagmus is caused by an interruption of the pathways connecting the posterior labyrinthine canals through the vestibular nuclei to the ocular motor nuclei. Causes include in particular the Arnold-Chiari malformation, cerebellar degeneration, and brainstem infarction. Downbeat nystagmus can also develop idiopathically in otherwise healthy people.

Pearl

Peripheral and central vestibular nystagmus underlie Alexander's law, which states that nystagmus increases with gaze in the direction of the fast phases.

Disorders of Vergence

Definition

Vergence movements (convergence and divergence) are binocular movements in opposite directions that serve to align the visual axes of both eyes, so that the images of objects located at the distance of fixation will fall onto corresponding retinal locations.

The supranuclear structures that are responsible for the control of vergence movements lie in the midbrain.

When a paralysis of convergence is found, the examiner must decide whether the eye movement disturbance is isolated or if there are also deficits in accommodation and/or in accommodative miosis. If all three are impaired, the problem is referred to as a paralysis of the near reflex.

Test of Convergence

Convergence can be tested by having the patient fix binocularly on a fingertip of his/her outstretched hand, held in the midposition, and then to move the finger tip slowly toward the tip of his/her nose, while maintaining single binocular vision. A normal response has both eyes converging symmetrically toward the midline plane, accompanied by symmetrical pupillary miosis.

Spasm of the Near Reflex

Definition

Spasm of the near reflex is characterized by prolonged and excessive binocular convergence, accommodation, and miosis.

Note

Spasm of the near reflex is occasionally mistaken for paretic strabismus. A misinterpretation can be avoided, if one notes during examination of an esotropia with a variable angle between the eyes, whether the pupils constrict with increasingly convergent positions (see also Chap. 10, ■ Fig. 10.8). A characteristic feature of spasm of the near reflex is that diplopia is intermittent, and that lenses to correct the accommodative myopia improve acuity.

When faced with a patient who shows the signs of spasm of the near reflex, the examiner must first consider whether the problem is psychogenic, since the pattern if innervation being examined can be volitionally driven. Spasm of the near reflex is often accompanied by voluntary nystagmus, a small angle, high-frequency quivering motion of the eyes. Dissociated end-gaze nystagmus is also frequently associated with spasm of the near reflex. Such volitionally controllable behaviors should not be taken for signs of organic pathology.

Spasm of the near reflex can spontaneously disappear. Occasionally, however, it is a tenacious disorder. Psychotherapy is often ineffective. As a last resort, one can atropinize both eyes and fit the patient with a pair of progressive addition lenses, fogging one eye to eliminate the diplopic symptom.

Congenital Nystagmus

Definition

Congenital nystagmus (CN) appears in many cases not at the time of birth, but rather in the third month of life, and might be better described as infantile nystagmus. There are both X-linked and autosomal dominant inheritance patters, but most cases are sporadic. CN is not ordinarily associated with general brain damage. By strict definition, cases classified as CN should include only those in which the eyes are otherwise normal. However, the following eight signs of CN are also valid for ocular nystagmus, which is due to ocular defects that are congenital or acquired in the first month of life. Thus, it is important for every case of CN to search for evidence of ocular malformations and/or early acquisition of ocular abnormalities (see "Ocular Nystagmus" below).

Video 11.4

Signs of CN

1. CN is not suppressed by fixation.
2. The pattern of beating is irregular: During the slow phases, the velocity of movement changes. Most cases show acceleration of the movement during the slow phases. Purely pendular movements are rare.
3. CN beats mostly in a purely horizontal motion that is retained in both upgaze and downgaze, but vertical, rotary, and mixed beating patterns are occasionally found.
4. In most cases, the intensity of the nystagmus and the shape of the slow phases change with gaze direction. The position of gaze where movement is minimal is variously called the neutral point, the quiet point, or the null point. The patient prefers this gaze direction. If the null point is in the midline, the head will be held straight. If it is eccentric, a compensatory head posture will be present.

5. In most cases, CN diminishes with accommodative convergence.
6. OKN stimuli frequently evoke saccades in the direction of stimulus movement, instead of slow nystagmus phases.
7. Under everyday viewing conditions, patients with CN do not experience oscillopsia. However, during fixation of a point of light in an otherwise darkened room, oscillopsia can appear.
8. Nutation (involuntary head nodding or shaking) is frequently seen in patients with CN, particularly when they are under psychic stress.

Treatment of CN

Treatment options are very limited. In cases where the null point of nystagmus is eccentrically located, the compensatory head posture can be relieved through surgical repositioning of the null point to the primary position (the Kestenbaum procedure). For many patients who experience dampening of the nystagmus during accommodative convergence, fusional vergence has a favorable effect. It can be tested by using base-out prism lenses in a trial frame to see whether fusional convergence is useable. For those with positive prism tests, surgical creation of an exophoria can be helpful for reducing the nystagmus and improving acuity. Controversially discussed are surgical procedures like destroying presumed proprioceptors at the insertion of the eye muscles, or weakening of all muscles that operate in the plane of the nystagmus.

Ocular Nystagmus

Definition

Ocular nystagmus is due to ocular defects that are congenital or have been acquired in the first weeks of life. Ocular nystagmus shows similar motor characteristics as congenital nystagmus with normal eyes.

The most common ocular changes that lead to nystagmus are lens opacities, macular scars (e.g., toxoplasmosis), retinopathy of prematurity, optic nerve hypoplasia, and macular hypoplasia. Macular hypoplasia is recognized by an absence of the ring and central reflexes of the inner retinal surface, as seen during ophthalmoscopy. There is also absence of an identifiable foveola. Macular hypoplasia is associated most commonly with albinism, rod monochromacy, and aniridia. In the X-linked hereditary incomplete form of congenital stationary night blindness, it is primarily rod vision that is defective, although cone vision is also partially reduced, which can contribute to the development of nystagmus.

Note

Every diagnosis of presumed CN should initiate an intensive search to rule out primary ocular defects.

Lesions to the posterior (retrogeniculate) visual pathways do not cause nystagmus

Latent Nystagmus

Definition

Latent nystagmus has acquired its name due to the fact that it is completely hidden or only slightly visible under normal viewing conditions. With monocular occlusion, however, the nystagmus appears or increases. Under occlusion of the right eye (and the left eye fixing) both eyes beat to the left, and under occlusion of the left eye (and the right eye fixing) both eyes beat to the right. This reversion of nystagmus direction on alternate fixation of the eyes is the defining characteristic of latent nystagmus.

Latent nystagmus is found almost exclusively in association with infantile forms of strabismus. Thus, the detection of latent nystagmus marks the case as one in which the patient has had a strabismus since early childhood.

Pearl

Subtle latent nystagmus is most reliably demonstrated with the monocular ophthalmoscopic fixation test (the other eye must be occluded).

Acquired Fixation Nystagmus

Definition

Any nystagmus that is not suppressed by fixation can be called a **fixation nystagmus**.

Congenital, ocular, and latent forms of nystagmus are constitutional and develop within the first few weeks of life. A nystagmus with a beating pattern similar to that of CN can also be **acquired**, most commonly in a clinical setting of known or suspected multiple sclerosis, but also less commonly associated with cerebrovascular disease and angioma. Nevertheless, the diagnosis of CN in the presence of its associated signs and symptoms is hard to miss.

Video 11.5

Pearl

Fixation nystagmus in patients with multiples sclerosis can cause severe oscillopsia. The medication memantine can suppress this form of nystagmus.

Spasmus Nutans

Definition

Spasmus nutans is a nystagmus that begins in the first year of life, and then after 1 to 2 years (occasionally longer), largely disappears. Spasmus nutans usually has a high frequency (above 7 Hz) and small amplitude. The oscillation is pendular and mostly horizontal, but vertical and rotary components can be present.

Not infrequently, spasmus nutans is asymmetric, and this often gives the impression that only one eye is oscillating. In many cases, spasmus nutans appears only now and then. Children with this disorder often have a wobbling or nodding head movement (*nutare*, to nod). The frequency of the head movement is about 3 Hz and is notably slower than the nystagmus

The cause of spasmus nutans is unknown. The diagnosis can often be made in retrospect, if the nystagmus has largely disappeared.

CN can be distinguished from spasmus nutans, which has a higher frequency and a noticeably asymmetric appearance. In contradistinction to CN, OKN in patients with spasmus nutans functions normally.

Pearl

Spasmus nutans can be confused with the nystagmus of a glioma in the chiasmal region.

Video 11.6

The differential diagnosis of spasmus nutans requires an MRI when one of the following signs implicates a chiasmal glioma: a vertical and alternating beating pattern like that of see-saw nystagmus, optic atrophy, a relative afferent pupillary defect, other distinctive neurological features, or hydrocephalus found by ultrasound exam.

Saccadic Oscillation

Definition

Saccadic oscillation is characterized by quick, involuntary eye movements, which interrupt fixation.

Saccadic oscillation should not be confused with nystagmus – nystagmus is initiated by slow eye movements, saccadic oscillation by fast eye movements. During the saccadic oscillation, the individual saccades can be separated by an interval, or may not. The back and forth movements often appear in bursts. The most striking form of saccadic oscillation is opsoclonus, in which the eyes continuously execute large, random saccades in horizontal, vertical and oblique directions.

The locus of damage responsible for opsoclonus is not known. Causes of this ocular motor pathology include encephalitis and paraneoplastic immune responses. Among children, a neuroblastoma should be suspected, and among adults, carcinomas of the lung, breast, uterus, bladder, and thyroid gland.

Conclusion

When dealing with an eye movement disorder, the first order of business is to establish the anatomic location of pathology. It is the ophthalmologist's task to differentiate supranuclear from infranuclear eye movement disorders. Supranuclear disorders are characterized by selective impairment of individual kinds of eye movement. To form a differential diagnosis all types of eye movements must be tested: goal-directed saccades, pursuit movements, optokinetic nystagmus, VOR, and accommodative convergence. The respective diagnostic tests are not time consuming. Their results help determine the probable locus of disease and guide the examiner's attention to relevant features of the clinical history. With this information in hand, high resolution imaging (CT and/or MRI scans) can be aimed at the clinically suspected area of damage. This strategy will improve the efficiency of the workup and help with identifying the nature of the pathology (■ Fig. 11.2).

Further Reading

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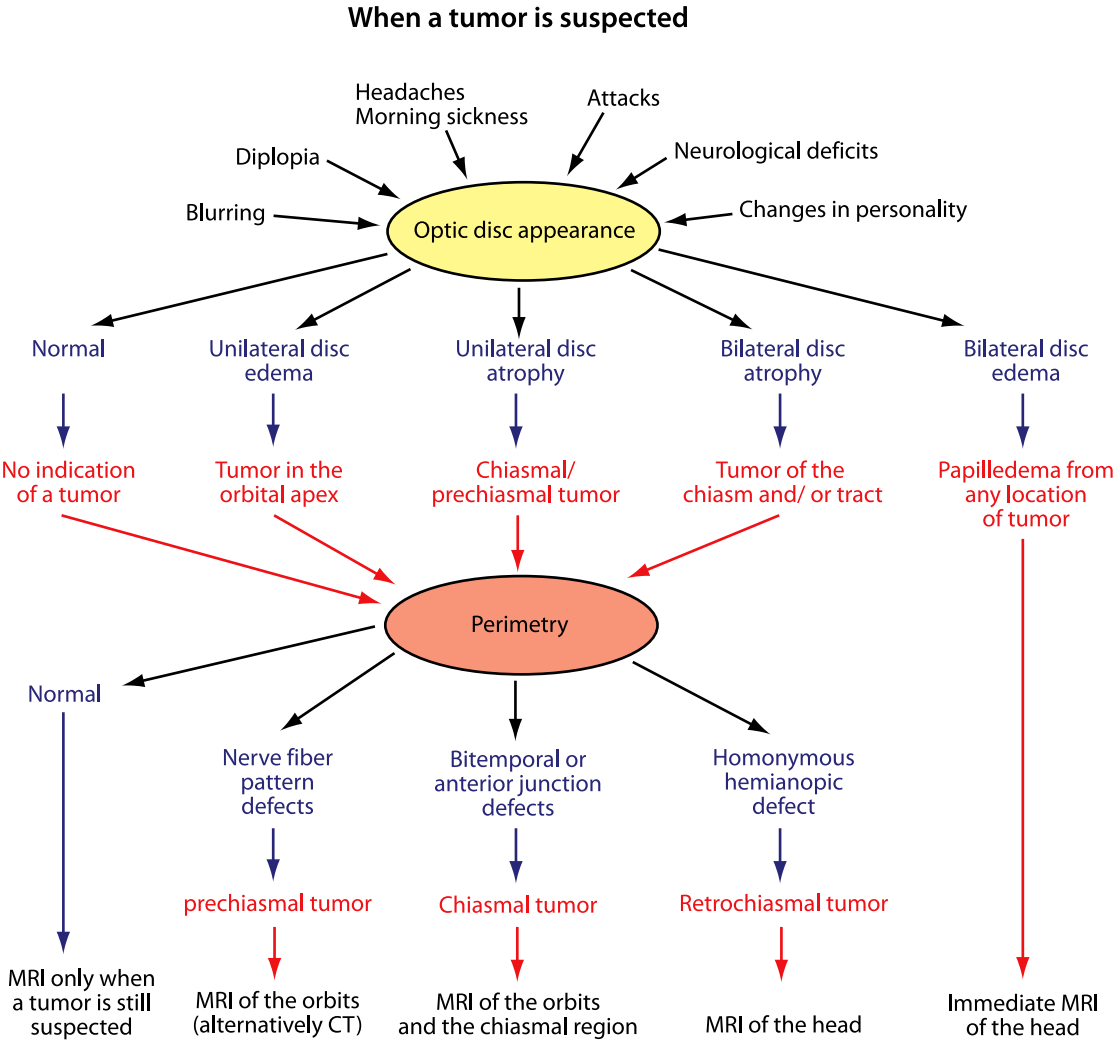
Brain Tumors Relevant to Clinical Neuro-Ophthalmology

B. Leo-Kottler

The ophthalmologist should keep in mind that the differential diagnosis always includes the chance that a brain tumor might be at fault. It is not at all unusual for these potentially life-threatening diseases to present with purely ophthalmologic symptoms.



Classification and Significance of Solitary Brain Tumors

Definition

Brain tumors as a group are meant to include all intracranial masses that arise from the brain parenchyma or other structures within the intracranial space.

The classification of brain tumors derives from the tissues of their developmental origins and is divided into neuroepithelial, mesodermal, and ectodermal tumors, as well as developmental malformations and metastases.

The importance of individual tumor types stems from their relative frequency. Included among neuroepithelial tumors (■ Table 12.1), glioblastomas, oligodendrogliomas, astrocytomas, pilocytic astrocytomas, and neurinomas are the most common. The mesodermal tumors encountered most frequently are the meningiomas, and the most common ectodermal tumors are pituitary adenomas. A fourth group, not belonging to the tridermic tumors, are developmental malformations, such as craniopharyngiomas and germinomas, and a fifth group is included for classification of intracranial metastases.

Table 12.1. Brain tumors of neuroepithelial origin

Glioblastomas
Oligodendrogliomas
Astrocytomas
Pilocytic astrocytomas
Neurinomas
Ependymomas
Medulloblastomas
Rarely: Choroid plexus papillomas, pinealomas, gangliocytomas

Pearl

Fifteen to 20% of all brain tumors are located in the region of the chiasma, and of these 50% are pituitary adenomas, 25% are craniopharyngiomas, 10% meningiomas, and 5% gliomas.

Symptoms of Brain Tumors

Pearl

Half of all patients with brain tumors have ophthalmic signs and/or symptoms.

The position of tumors in the intracranial space determines their associated, focal signs, and symptoms. Often, however, it is not the focal disturbance that catches attention, but the distant effects of tumors (such as obstruction to the flow of cerebrospinal fluid) that determine the patient's earliest symptoms. The historical time course of symptoms gives the examiner clues to the tumor's rate of growth. The patient's age makes certain tumor types more likely than others (■ Table 12.2). Therefore, a pituitary adenoma in a child is rare, but a craniopharyngioma as the source of a pediatric chiasmal syndrome is far more likely.

Table 12.2. Brain tumors, by life stages

Children, adolescents	Cerebellum and brain stem: medulloblastomas, pilocytic astrocytomas, ependymomas Chiasmal region: optic nerve gliomas, craniopharyngiomas
Middle-aged	Meningiomas, astrocytomas, oligodendrogliomas, pituitary adenomas, neurinomas
Elderly	Glioblastomas, metastases

Typical Signs and Symptoms of Brain Tumors

Typical signs and symptoms of a brain tumor include headache, neurological deficits, psychic changes (the patient and his/her relatives are usually unaware of these changes or misjudge them as trivial, especially when they have developed gradually) epileptic attacks, and visual symptoms (■ Table 12.3).

Table 12.3. Typical ophthalmologic signs and symptoms of brain tumors

Loss of vision
Optic disc changes (optic atrophy, papilledema)
Motility disorders (third, fourth and sixth cranial nerves)
Exophthalmos
Visual field defects
Loss of color vision (desaturation)
Loss of somatic sensation (fifth cranial nerve)

Note

An epileptic attack occurring in a patient past the age of 20 years with no prior history of epilepsy should raise the suspicion of a tumor.

Brain tumors that cause visual symptoms usually do so by compressing portions of the anterior afferent (pregeniculate) visual pathway. In the ophthalmic evaluation of such patients, the examination of even subtle changes in the visual field is of paramount importance (see Chap. 4). Such changes also give guidance when studying potential effects of brain tumors on the postgeniculate visual pathways (the optic radiations).

Examination Methods to be Used When a Brain Tumor is Suspected

If the abovementioned signs and symptoms raise the suspicion of a brain tumor, the following tests of visual function are particularly important:

- The visual acuities of both eyes with the best possible optical correction
- Testing for a relative afferent pupillary defect
- Careful perimetry of both eyes (pay particular attention to sign of an anterior junction syndrome; see Chaps. 3 and 4)
- Examination of ocular motility
- Fundus examination with particular attention to the optic discs, comparing one side to the other

Pearl

Additional tests during the examination should include visually evoked potentials, exophthalmometry, the testing of corneal touch sensitivity, and olfactory sensation.

Imaging by CT or MRI is mandatory, with the method of choice being the MRI. If the tumor is thought to invade, adhere to, or erode through bony structures, a CT scan can be added. The CT is also helpful when the tumor is associated with the formation of calcific deposits, as is typical for optic nerve sheath meningiomas (and pediatric retinoblastomas).

Metastasis of Brain Tumors

An intracerebral metastasis of a brain tumor is significantly more frequent than an extracerebral spread. Its tendency to spread is favored by elevated intracranial pressure, and it tends to seed areas where the flow of cerebral spinal fluid (CSF) is slow. Medulloblastomas and pineal tumors are particularly likely to behave this way. Typical are the so-called drop metastases within the spinal canal.

Pearl

Extracerebral metastases of brain tumors are very uncommon.

Metastasis is known to increase in likelihood following operative procedures (at the site of the sentinel tumor) and is most frequent among medulloblastomas, ependymomas, glioblastomas, and occurs much less commonly among meningiomas. Frequent sites for extracranial metastatic spread of brain tumors include the tissues of bone, lung, and lymph node.

Tumors of the Pregeniculate Afferent Visual Pathway

Tumors arising from the tissues of the pregeniculate afferent pathway can be classified as:

- Tumors arising from a component cell type of the optic nerve
- Tumors that develop from the sheaths of the optic nerve
- Tumors that arise from the tissues of surrounding structures
- Tumors due to the infiltration of malignant cells inside the optic nerve sheaths, or between the ganglion cell axons themselves

The clinical signs and symptoms of tumors affecting the optic nerves, the chiasm, and the optic tracts differ significantly from one another, depending on which of these segments they have damaged.

Signs and Symptoms of Tumors in the Pregeniculate Afferent Visual Pathway

Compression Syndromes

The development of a compression syndrome of the pregeniculate visual pathway should always suggest the possibility of an intracranial tumor, no matter which segment of the path is involved (nerve, chiasm, tract) or at what rate it has developed (acute, subacute, or slowly progressive).

Compression syndromes damage the afferent path by the mass effect of the pressure they exert on the involved segment. This can be caused by neoplasms, hemorrhages or obstruction to CSF flow (e.g., aqueductal stenosis), and causes ischemic damage to the ganglion cell axons. An

acute compression syndrome is characterized by a dramatic fall in visual acuity, acute development of defects in the visual fields (e.g., acute bitemporal hemianopia), afferent or efferent disturbances of pupillary function, and acute cranial nerve palsies.

Typical for chronic compression syndrome, on the contrary, are insidiously developing and frequently unnoticed loss of acuity, loss of color perception (red/green desaturation), a relative afferent pupillary defect, exophthalmos, cranial neuropathies, and visual field defects.

Signs and Symptoms of Tumors in the Prechiasmal Segment of the Afferent Visual Pathway

Tumors of the prechiasmal segment of the afferent visual pathway are typically unilateral (and for that reason often unnoticed), cause a fluctuating acuity deficit from day to day, and have a slow rate of progression. Monocular visual deficits that vary with the direction of gaze are frequently a sign of a retrobulbar mass, such as a hemangioma or an optic nerve sheath meningioma. Frequently an associated loss of color saturation, especially for red colors, also escapes the patient's notice. (Reds acquire a faded-orange or brown color.) Classically, monocular visual field defects develop, with features that vary according to the location of the compression. Early signs and symptoms often include mild unilateral proptosis, a change in eyelid position, and/or a restriction of ocular movements. Pain is very uncommon. There is commonly a relative afferent pupillary defect on the affected side, often combined with a varying degree of optic disc atrophy. Obstruction of normal axoplasmic flow by mass compression of the optic nerve fibers commonly causes a unilateral form of optic disc swelling, as can also happen with direct neoplastic infiltration of the optic disc. A chronic, slowly progressive compression (typical for optic nerve sheath meningiomas) causes the formation of optociliary shunts (■ Fig. 12.1) that provide an escape path for retinal venous blood that cannot exit through the compressed central retinal vein, allowing it to enter the choroidal vessels and exit the eye via the vortex veins. Large, rapidly growing infiltrating neoplasms with spread into the surrounding structures can cause diplopia by mechanical displacing or directly infiltrating the extraocular muscles. Such processes also cause an exophthalmos effected by axial proptosis of the globe, driven by a growing retrobulbar mass. Compression of the ocular wall can cause folds of the retina and choroid to appear (■ Fig. 12.2).

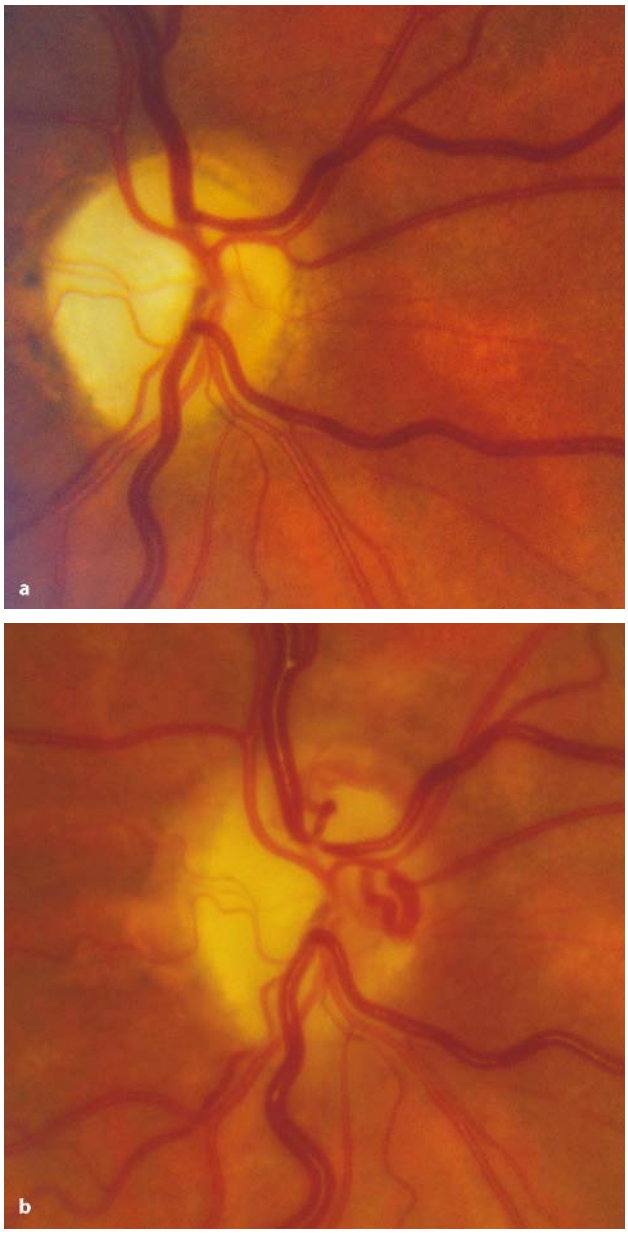


Fig. 12.1. **a** Development of optociliary shunt vessels on the optic disc, caused by optic nerve sheath meningioma. Initial findings. **b** Development of optociliary shunt vessels on the optic disc. Four years had elapsed between the time **a** and **b** were taken

Signs and Symptoms of Tumors Affecting the Chiasmal Region of the Afferent Visual Pathway

The pathognomonic signs of chiasmal disease include bilateral, usually bitemporal, visual field defects that respect the vertical meridian (see Chaps. 3 and 4). The bitemporal character of the visual loss and typical course of isopters with sharply defined discontinuities at the midline are easily detected with kinetic perimetry in the central 30° of the field, but discrete defects are more accurately demonstrable by automated static perimetry.

Fig. 12.2. Compression of the posterior pole with choroidal and retinal folds, caused by an optic nerve sheath meningioma

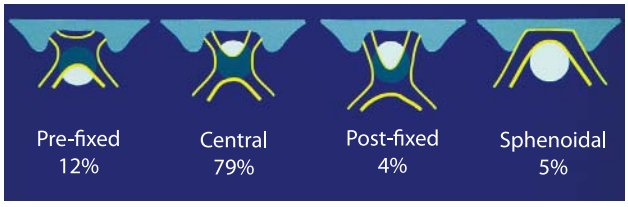


Fig. 12.3. Positional relationships between the chiasm and the pituitary gland, underlying the variations in visual field defects caused by chiasmal compression

Table 12.4. Space-occupying diseases in the sellar and suprasellar region

	Pituitary adenomas
Tumors thought to arise from sequestered groups of undifferentiated cells	*Craniopharyngiomas* Epidermoid cysts Chordomas
Germ cell tumors	Germinomas Teratomas Dysgerminomas Ectopic pinealomas
Other tumors	*Meningiomas* *Optic nerve gliomas* Astrocytomas
Metastases	Breast carcinomas Bronchogenic carcinomas Renal cell carcinomas

Pearl

Tumors that arise from positions inferior to the chiasm, such as those arising from the pituitary gland, initially produce deficits with a bitemporal component in the superior quadrants, close to the midline. Other tumors, like the craniopharyngiomas that approach the chiasm from above, are more likely to cause early bitemporal deficits that first appear in the lower quadrants (see Chaps. 3 and 4).

More important for the nature of early visual field defect, however, is the positional relationship between the chiasm and the diaphragma sellae. This varies significantly from one person to the next (■ Fig. 12.3). Compression of the chiasm by masses approaching from the anterior aspect are more likely to cause monocular or highly asymmetric visual field loss, while tumors that compress the posterior aspect of the chiasm are more likely to cause homonymous patterns of loss by damaging the optic tract(s). Tumor types are summarized in ■ Table 12.4 (particularly frequent types are in italics).

The extent of visual field loss at the time of diagnosis varies from (1) minimal deficits that the patient has not yet noticed to (2) complete bilateral loss of the temporal hemifields to (3) catastrophic, binocular loss of all light perception. The latter presentation is seen when necrosis of and subsequent hemorrhage into a rapidly growing pituitary adenoma results in pituitary apoplexy, an abrupt enlargement of the tumor that causes intense headache and acute, severe compression of the chiasm from below. Rapid surgical decompression of the chiasm by evacuating the mass often allows for substantial recovery of the acutely lost vision. Bilateral loss of the temporal hemifields causes a loss of depth perception, with a completely blind area beyond the object of regard and loss of fusional vergence control (due to loss of all binocular areas of visual field). The loss of motor control of ocular alignment due to the loss of all binocular areas of the visual field results in sensory disturbances that include absolute blind areas between separated nasal hemifields (in patients with antecedent esodeviations), diplopia with overlapping nasal hemifields (antecedent exodeviations), or splitting and relative vertical displacement of image halves in those with vertical heterophorias (the so-called hemifield slide phenomenon described in Chaps. 2 and 15). Acuity is not necessarily reduced but will more likely to appear the longer the process lasts and the deeper the visual field loss grows. Even in the early stages of chiasmal progression, the acuities of both eyes may be reduced. Compression of the chiasm is usually blunt, with large masses with smooth surfaces, and damage is done to both crossing and uncrossed axons within the

chiasm. This explains the loss of acuity in chiasmal disease and retention of normal acuity in patients with complete, retrogeniculate, homonymous hemianopias.

Optic atrophy may or may not be seen at the time of presentation, but is usually affecting both eyes (one exception: anterior junction syndrome, discussed in Chap. 3), a sign that the chiasmal damage is part of a long-standing disease process.

! Note

The extent of optic atrophy does not correlate with the extent of acuity loss. Even bilateral optic atrophy does not always rule out a possible recovery of both Snellen acuity and visual field. However, disc pallor does suggest that the recoverability of optic nerve and chiasmal function after surgical decompression is limited.

Development of papilledema caused by chiasmal/perichiasmal disease is very uncommon but does occur when the mass compresses and obstructs the foramina of Monro. This can happen when a large mass compresses and invades the third ventricle from below. Suprasellar masses like the craniopharyngiomas (particularly in children) are more likely to cause papilledema before the atrophy sets in. Combined appearances of both edema and atrophy in the optic discs are a good indication that both acute and chronic disease processes are at play.

When a tumor is suspected in the chiasmal region, it helps to inquire about nonvisual symptoms that suggest damage to the hypophysis, e.g., diabetes insipidus via compression of the supraoptic and paraventricular nuclei of the diencephalon (■ Fig. 12.4). This alters the level of antidiuretic hormone (ADH), causing excretion of dilute urine in large volumes, and a persistent thirst with a marked increase in water consumption. Diabetes insipidus is particularly common in patients with craniopharyngiomas, gliomas of the hypothalamus, and germinomas. Disturbances of pituitary function because of compression of the adenohypophysis are common and are more likely to be encountered in women than in men. A slowly developing insufficiency of the anterior lobe of the pituitary gland is usually associated with a drop in gonadotropic hormones, causing amenorrhea in women of childbearing age. This is often a presentation of chiasmal disease, although it is often first discovered by endocrinologists. A comparable hormonal syndrome occurs in men, with a loss of libido and erectile function, which is frequently assumed nonpathological. The tumors in men are on average larger than are those in women. This holds true for prolactinomas, which in women cause a galactorrhea and amenorrhea, and which in men usually cause a primary loss of libido and erectile function.

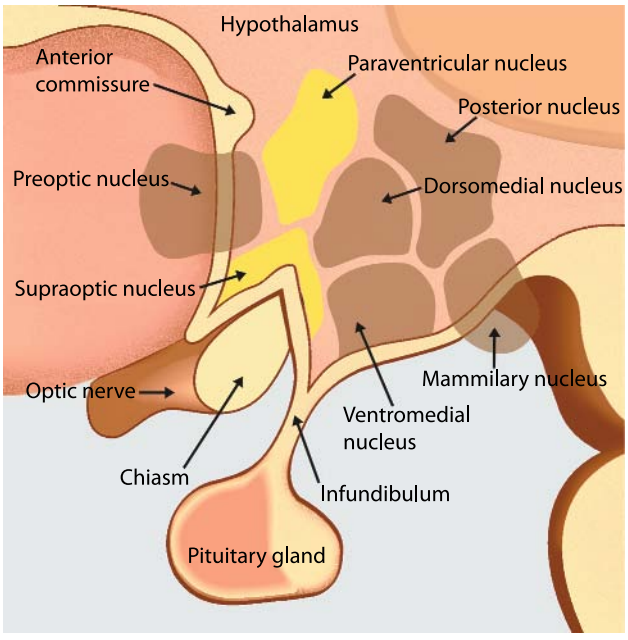


Fig. 12.4. Diagrammatic view of the hypothalamic nuclei located superior to the chiasm (the supraoptic nucleus and the paraventricular nucleus), which are the first to be compressed by expanding tumors arising in the midline from beneath the chiasm (modified after Netter)

! Note

Disease processes in the diencephalon are also marked by abnormally low growth rates and behavioral disorders, and when delayed growth in children is paired with optic atrophy, a tumor in the chiasmal region should be suspected.

When a tumor enlarges eccentrically to one side, it can invade the cavernous sinus, with corresponding clinical signs and symptoms (chiefly multiple cranial nerve palsies; see Chap. 10).

Signs and Symptoms of Tumors Affecting the Optic Tracts

Chiefly, the sign of a tumor compressing the optic tract is a poorly congruous, homonymous visual field loss (see Chap. 4) with a relative afferent pupillary defect (RAPD) in the eye that has lost its temporal hemifield, i.e., contralateral to the side of the damaged tract, with asymmetrical optic atrophy (see Chap. 8, ■ Fig. 8.23 and Chap. 19, ■ Fig. 19.6).

In addition, this presentation is frequently associated with focal signs and symptoms of neurological disease. Depending on the locus and extent of damage to structures near the optic tract, these focal problems often precede the correct diagnosis of an intracranial tumor and should indicate to the physician that a closer evaluation is needed.

Specific Signs and Symptoms of Brain Tumors Relevant to Clinical Neuro-Ophthalmology

Optic Nerve Gliomas (Pilocytic Astrocytomas)

Three groups of optic nerve gliomas are differentiated according to their distributions:

1. Confined to the optic nerve on one side.
2. Damaging the chiasm (a more frequent situation than the monocular form). Twenty-five percent of optic nerve gliomas have already reached the chiasm by the time of their discovery.
3. Involving the hypothalamus and the region of the third ventricle. Thirty percent of these patients have hydrocephalus.

Optic nerve gliomas are uncommon. Only 1 to 2% of all gliomas are found in the optic nerve. However, optic nerve gliomas represent 2 to 5% of all brain tumors in children. Among children and adolescents the glioma is a common tumor of the pregeniculate pathway and is especially frequent (6.6 to 20%) in patients with neurofibrosis type I (located on chromosome 17q11.2). Children under 6 years of age are at the greatest risk of developing symptomatic optic nerve gliomas. Lisch nodules of the iris are an important diagnostic clue (see Chap. 19). There is a significant gender difference, with girls and women more often affected than are boys and men.

Signs and Symptoms of Optic Nerve Gliomas

A common presentation includes exophthalmos with strabismus of the affected eye, associated with a loss of visual acuity, visual field defects, optic atrophy, and a relative afferent pupillary defect. Not infrequently, an acquired nystagmus is the first clinical sign. The most common sign is optic atrophy on the affected side, and bilateral involvement is not uncommon. The mass grows slowly and advanced stages of enlargement are commonly associated with diencephalic disorders, including diabetes insipidus, adiposity, delayed sexual maturation, and somnolence.

Treatment of Optic Nerve Gliomas

Treatment of these tumors is controversial. For those tumors that are confined to the intraorbital course of the optic nerve with complete loss of vision in the affected eye, options include surgical extirpation of the tumor (resection of the involved segment of the nerve), radiation therapy, and observation. The latter choice might be appropriate in the absence of pain with no significant disfigurement. For young children of less than 5 years of age who have demonstrable progression of chiasmal tumors the use of radiotherapy is to be avoided, since they have higher risks of associated morbidities, especially malignancies occurring later in the tissues exposed to the radiation. In these cases, chemotherapy is now preferred. Gliomas that are found in the hypothalamus seem to have a more favorable course following radiotherapy, rather than being simply observed. The differences are not great, however, and some still advocate conservative observation, particularly if serial MRI scanning shows stability of the tumor's size.

Pearl

A phase of initially rapid growth, followed by years of stable size, is typical for optic nerve gliomas.

Pituitary Tumors

Pituitary tumors are most frequently prolactinomas (35%), less commonly somatotropin-secreting tumors (25%), and even less commonly adrenocorticotrophic hormone (ACTH)-producing tumors (5%). Sporadically, tumors that produce thyroid-stimulating hormone (TSH) or gonadotrophins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) are seen. In some cases, a pituitary adenoma causes overproduction of several hormones.

Pearl

About two thirds of all pituitary tumors have some degree of endocrine-secreting activity, while the remaining third are said to be silent.

Middle-aged adults are most frequently affected by pituitary tumors (about 12 to 15% of all intracranial neoplasms), while children are seldom found to have primary pituitary adenomas. Both sexes are equally represented.

Pearl

Only 30% of patients presenting with pituitary tumors complain of visual problems. The tumor must rise more than 1 cm above the diaphragma sellae before causing a clinically detectable loss of visual field and/or acuity. Commonly, this is a hormonally inactive tumor that due to the absence of endocrine signs or symptoms has been very inconspicuous.

Pituitary microadenomas are those with a diameter of 10 mm or less. The threshold for radiological detection of a microadenoma is 3 mm or less. A macroadenoma is spoken of, when the tumor's diameter amounts to more than 10 mm.

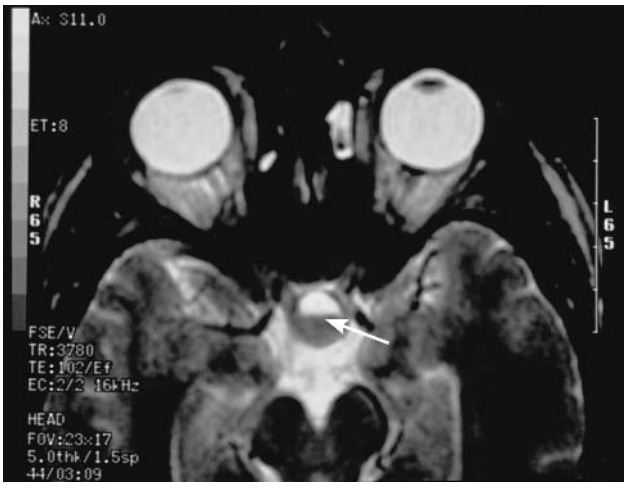


Fig. 12.5. Pituitary apoplexy. The level boundary within the tumor corresponds to the superior margin of the hemorrhage (*arrow*)

Signs and Symptoms of Pituitary Tumors

The most common ophthalmological sign of a pituitary adenoma is the bitemporal loss of visual field (see Chaps. 3 and 4). Fundus findings are at most (and often subtly) optic disc pallor. A loss of visual acuity is not always present (see above). Disturbances of motility involving dysfunction of the trochlear or abducens nerves are found in only about 10% of patients. With very large, eccentrically growing tumors, there is occasionally damage to the first two branches of the trigeminal nerve.

Pituitary Apoplexy

see also Cases TES 1.1

Occasionally (at most, 10% of cases) a pituitary tumor will present as an abruptly expanding mass with an intralesional hemorrhage, brought on by ischemic necrosis when the rapidly proliferating tumor outgrows its available blood supply (■ Fig. 12.5).

During pregnancy, there is a higher risk to vision from an accelerated rate of tumor growth. Pregnancy, trauma, prior radiation therapy, and defects in blood coagulation all increase the risk of pituitary apoplexy.

Treatment of Pituitary Tumors

For microadenomas, which cause no problem with vision, treatment is directed at relieving any hormonal imbalances. For macroadenomas with hormonal activity, medical therapy must usually be accompanied by some degree of surgical reduction in the size of the mass. Favorable effects can occur within 24 h of surgical decompression, after several days of medical management (e.g., bromocriptine, see below), or several months after radiotherapy.

The differential diagnosis of a pituitary adenoma should always include mention of secondary pituitary enlargement. A primary deficit of a pituitary end organ's hormonal production (e.g., primary hypothyroidism) could cause a secondary swelling of the pituitary gland of sufficient size to make contact with the chiasm. In such cases, simple replacement of the missing hormone will lead to a reversal of the syndrome.

! Note

No surgery should be considered for a pituitary tumor prior to a complete endocrinological evaluation.

Prolactinoma

A prolactin-secreting tumor of the pituitary gland can cause a dramatic hyperprolactinemia. One third of all hyperprolactinemias are caused by hypersecreting tumors of the pituitary, and the prolactin level in serum rises to above 200 ng/ml. Typical clinical symptoms are amenorrhea and galactorrhea among women, and loss of libido and erectile function in men, and less commonly, gynecomastia. Prolactinomas in women, who are often alarmed by the endocrinological changes, are usually microadenomas, and are not usually associated with optic disc pallor or visual field defects.

● Pearl

Men often have large prolactinomas with chiasmal compression. It is thought that men commonly repress or ignore the symptoms until late in the course of the tumor's development.

Treatment is tailored according to the size of the tumor. Surgery is indicated in most cases that have:

1. A suprasellar macroadenoma with chiasmal compression.
2. A suprasellar macroadenoma without chiasmal signs or symptoms, but planning for a pregnancy. During pregnancy, prolactinomas can enlarge considerably in 35% of cases.
3. A suprasellar macroadenoma without chiasmal damage, but the patient is intolerant of treatment with dopamine agonists.

If there are no definite indications for surgical intervention, the use of dopamine agonists, e.g., bromocriptine (Parlodel) at doses of 2.5 to 5 or 7.5 mg daily is usually successful. Seventy-three of prolactin-secreting tumors treated with bromocriptine shrink, and in 95% of cases, the blood levels of prolactin will return to normal levels. The drug will show an improvement in symptoms within 72 h of initiating its use. However, it will cause nausea, vomiting, hypotension, and vasospasms in higher doses. Cautious use of lower doses of bromocriptine can usually be toler-

ated without losing its effectiveness for normalizing prolactin levels and reducing the size of the tumor. Alternatively, cabergoline (Dostinex), 0.5 mg, can be given twice weekly, with better tolerance among some patients. Additionally there is a definite risk of tissue necrosis developing during treatment, which can lead to a pituitary apoplexy that requires emergent neurosurgical intervention for its proper management. In addition, tumors can erode the floor of the sella, and when shrinking under the effects of bromocriptine, a CSF leak can develop with an increased risk of bacterial meningitis.

Somatotrophic Hormone–Producing Pituitary Tumors

Endocrinologically these tumors are characterized by elevated production of somatotrophic hormone (STH). The excessive production of growth hormone produces in (preferentially male) children and adolescents with as yet unclosed epiphyses accelerated growth of long bones that can lead to gigantism, whereas among adults (here the female sex is more commonly affected) the effect is to produce acromegaly: enlargement of the acral body parts – nose, chin, fingers and toes with enlargement also of abdominal organs and a deepening of the voice.

The treatment of STH-producing tumors must take a surgical approach, which can usually be done by a transsphenoidal approach (see Chap. 22). For intrasellar tumors, the success rate approaches 90%. In cases where surgery is not possible, analogs of somatostatin are an effective alternative. These agents can normalize the STH levels in 90% of cases, improve the symptoms in 50% of cases, and reduce the size of the tumor in 44% of cases. Initial studies of treatment of acromegaly with a growth hormone receptor antagonist pegvisomant (Somavert) seem encouraging. This drug is used under tightly restricted access in the United States, and access is provided on a case-by-case basis. A trial of treatment with dopamine agonists can be made. Radiation is not useful, since years can pass before the blood levels of growth hormone are reduced. The consequences of STH overproduction include an increase in morbidity that is partly irreversible.

ACTH-Producing Pituitary Tumors

The endocrinological effects of elevated ACTH levels are clinically expressed as Cushing's syndrome (moon face, torso adiposity, diabetes mellitus, and muscle atrophy). The surgical management of ACTH-producing tumors is challenging. Not uncommonly, there is a diffuse growth, often extra glandular, with the source of overproduction of the hormone being located in a microadenoma positioned eccentrically in the pituitary recess. Surgical success is attained in 70 to 90% of cases. Alternatively, treatment with the antiserotonin cyproheptadine results in a clinical remission in 50% of cases. Equally likely is a reduction in the rate of cortisol synthesis by treatment with ketoconazol. For relapses, radiation therapy should be considered.

Endocrinologically Silent Pituitary Adenomas

Hormonally inactive pituitary tumors (up to one third of all pituitary tumors) can with growth and displacement of surrounding tissues result in a hormonal deficit, hypopituitarism with a loss of gonadal function (often the first clinical sign) and hypothyroidism, weakness of the muscles, loss of body hair or with symptoms of hypothalamic disease, including diabetes insipidus, and disorders of sleep, body temperature, and poor motivation.

Chiasmal syndrome is particularly frequent among cases of hormonally inactive tumors, since they are as rule large by the time the correct diagnosis has been made. Regressive changes are more frequent, also due to the large size of these tumors (cysts, necrosis, acute intralesional hemorrhages, and acute chiasmal syndrome). Surgical intervention is often necessary, but the large size and asymmetric extension of these tumors requires an approach by way of a craniotomy. Subtotal resection of the tumor should be followed by targeted radiation therapy.

Craniopharyngiomas

There are two theories to explain the origin of craniopharyngiomas. One assumes that the tumor cells arise from Rathke's pouch, the other that the cells arise through metaplasia of cells in the anterior lobe of the pituitary gland. Tumors with primary intrasellar growth are distinguished from those with the more common behavior of primary suprasellar growth.

One to 4% of all brain tumors are craniopharyngiomas, meaning that they are not common. Craniopharyngiomas among children, however, are second only to optic nerve and/or chiasmal gliomas as a cause of chiasmal syndrome. The incidence of craniopharyngiomas as a function of age is biphasic. Two thirds of all cases are found in patients less than 30 years of age, while adults between 50 and 70 years of age make up most of the remainder. Both sexes are equally represented.

Signs and Symptoms of Craniopharyngiomas

At the time of initial discovery of craniopharyngiomas, especially in the smaller children who are unaware of or cannot easily describe their visual problems, the tumors are usually already over 3 cm in diameter. They grow steadily in size, leading in 19% of cases to a dorsal chiasmal syndrome, compressing the chiasm from a posterior dorsal

position (see Chaps. 3 and 4). Frequently these tumors contain within them cystic spaces that fluctuate in size, filled with viscous fluid that has the color and consistency of motor oil. They often cause fluctuating disturbances of acuity and the visual field, which has detectable defects in more than two thirds of cases. The ocular fundus shows at most an appearance of (sometimes mild) optic atrophy, or (mostly in children) frank papilledema. Acuity is sometimes, but not always reduced.

Pearl

The term acute craniopharyngioma refers to a rupture of the cystic component of the tumor, causing a sterile meningitis.

Calcifications appear in craniopharyngiomas in about 75% of cases. They usually present in company with signs and symptoms of hypothalamic compression. Diabetes insipidus is often present, and disorders of sleep, control of body temperature, and mental alertness are all present. Suprasellar growth of these masses is often heralded by the discovery of papilledema. A hydrocephalus is common in cases of suprasellar growth.

Treatment of Craniopharyngiomas

Surgical removal is the management of choice, but their removal is frequently subtotal, because the tumors, having a capsule of varying thickness, are often firmly adhered to surrounding neural structures. Postoperative radiation therapy following subtotal resections may be necessary.

Low-Grade Astrocytomas

The classification of astrocytomas of low-grade malignancy, as described in various textbooks of histopathology, covers a variable range of severity. A particular type is the pilocytic astrocytoma, found either in the cerebellum or (more frequently) the optic nerve (see above for a discussion of optic nerve gliomas).

About 30% of all gliomas are astrocytomas of low-grade malignancies. They appear in all age groups, but most commonly in men in the 20th to 50th years of life. The older the patient, the higher the grade of malignancy one can expect to find.

Signs and Symptoms Associated with Astrocytomas of Low Grades of Malignancy

Particularly frequent is the location of these tumors in the frontal and temporal lobes, especially in the deeper brain centers (e.g., the thalamus). They often have poorly defined borders in their early stages and are at first difficult to detect by neuroradiological imaging. They have a moderate rate of growth.

Pearl

Epileptic attacks are the presenting sign in 65% of patients.

If the afferent visual pathway is affected, there will typically be a slowly progressive homonymous hemianopia that evolves of a period of months (see Chap. 4), along with simultaneous, nonvisual neurological deficits.

Treatment of Astrocytomas of Low Malignancy

Primary treatment is always surgical. Because of the poor definition of the margins of these tumors, total removal is often impossible. In this case, postsurgical radiation therapy is indicated. Malignant transformation of these tumors due to the radiation therapy is not usually seen.

Gliomas of High Malignancy (Anaplastic Astrocytomas and Glioblastoma Multiforme)

Astrocytomas and glioblastomas can be distinguished from one another histologically. The malignant astrocytomas are highly anaplastic, while glioblastomas have multicolored staining properties. As many as 20% of cases present with signs of a multifocal genesis.

These tumors have a poor prognosis and constitute about half of all primary brain tumors found among middle-aged and elderly patients. Both sexes are equally affected. The patient's age at presentation is an important factor in the prognosis, which is significantly worse for patients over 50 years of age. Malignant gliomas most often arise in the cerebral hemispheres.

Signs and Symptoms of Highly Malignant Gliomas

Growth is rapid, causing a quick succession of multifocal and general neurological deficits, such as an abrupt onset and fast progression of visual field defects. Papilledema is often present, usually reverses its course following surgical intervention, and then reappears, along with a rapid relapse of the signs and symptoms of recurrent tumor growth.

Treatment of Highly Malignant Gliomas

Surgical resection of the mass, including a 2-cm layer of tissue beyond its apparent borders, is current practice, and is followed by irradiation with up to 60 Gy (these tumors are relatively radiation resistant). Additional chemotherapy with temozolomide (TMZ) should be considered a new standard of care for newly diagnosed glioblastoma

multiforme patients. Locoregional therapy with sustained delivery of BCNU (carmustine) from a biodegradable polymer placed around the resection perimeter at surgery (GLIADEL), radioimmunotherapy utilizing radiolabeled monoclonal antibodies against tumor-associated antigens and convection enhanced delivery (CED) – microinfusion catheters placed with stereotactic guidance in the peritumoral region to infuse a therapeutic agent over 3 to 5 days – provide important steps forward in clinical trials. Altogether, recent therapeutic advances have led to modest improvement in outcome for at least some malignant glioma patients. However, recurrence of these tumors can be expected.

Medulloblastoma

Medulloblastomas arise from immature, undifferentiated cells in the cerebellum. Histologically, a characteristic appearance is that of cells with round or elongated shapes that frequently form rosettes and (around blood vessels) pseudorosettes.

About 20% of pediatric brain tumors are medulloblastomas that in two thirds of cases arise during the first 15 years of life. The younger the child, the greater the aggressiveness of growth expected. There is a very high rate of local metastasis via the cerebrospinal fluid in the subarachnoid space, and a high rate of extraneural metastasis (30%). Sixty-five percent of cases are male, and in 90% of cases, the tumors arise in the posterior cranial fossa, most commonly in the cerebellar vermis.

Signs and Symptoms of Medulloblastomas

Internal hydrocephalus is common (40%), caused by obstruction to CSF flow in the region of the fourth ventricle, and there are frequently cerebellar signs, principally ataxia, and ocular findings commonly include papilledema.

Treatment of Medulloblastomas

Radical excision of the tumor is always necessary, followed by postoperative radiation therapy, including irradiation of the spinal canal to treat the so-called drop metastases. In children less than 3 years of age, after surgery chemotherapy is preferred.

Metastases

Between 4 and 20% of brain tumors are metastases. The type of metastases to be expected depends importantly on the patient's age: sarcomas (osteosarcoma, rhabdomyosarcoma) and germinal cell tumors of the testes in children, and carcinomatous metastases in adults (lung, breast, and renal cell carcinomas).

Signs and Symptoms of Intracranial Metastatic Disease

The signs and symptoms of brain metastases depend on the location of the metastatic growth, with the most common ophthalmic sign being papilledema caused by obstruction of CSF flow.

Treatment of Intracranial Metastases

Radical excision of solitary metastases, particularly those of renal cell carcinomas, can have a favorable result. Fifty percent of all patients with brain metastases die, in spite of "successful" surgical procedures, within 6 to 12 months.

Meningiomas

Several forms of meningioma are recognized: meningothelial, fibrous, and transitional are the most common subtypes. They arise ubiquitously. The growth can be nodular or *en plaque* (a laminar spread along the surface of the dura), and there are extracerebral manifestations. Forty percent are basal meningiomas, 50% are tumors of the convexities, and 10% are meningiomas of the posterior cranial fossa. In up to 16% of cases, meningiomas arise multifocally. Typically, there is a long, slow growth that can last for decades, often causing changes in the adjacent bone (an osteoblastic reaction, or so-called blistering), malignant transformation (2 to 10%), and metastasis formation (0.1%). Meningiomas often have a strong tendency to grow rapidly during pregnancy. The association of a meningioma with a carcinoma of the breast is not unusual.

Meningiomas may have a strong familial component. Several associated mutations or deletions on chromosome 22 have been identified. People suffering from neurofibromatosis type 1 and type 2 are at increased risk for the development of meningiomas.

Pearl

Meningiomas make up to 20% of all intracranial tumors. They are rare among children and adolescents; a patient age of 50 years is typical, with women being most frequently affected. Eighty-five percent of all meningiomas arise in women 40 to 60 years old.

Of primary ophthalmic importance are (1) optic nerve sheath meningiomas, (2) meningiomas of the tuberculum sellae, (3) meningiomas of the anterior clinoid process, and (4) sphenoid wing meningiomas. Intrasellar meningiomas are uncommon, rarely cause signs or symptoms and

are usually detected on MRI scans done for unrelated reasons.

Optic Nerve Sheath Meningiomas

Sheath meningiomas of the optic nerves arise either primarily from meningeal cells within the orbit or in the optic canal, or are an extension of intracranial meningiomas that are invading the optic canal. Women in the fifth decade of life are most often affected. Sheath meningiomas also occur in children, where their behavior is one of aggressive growth.

Signs and Symptoms of Optic Nerve Sheath Meningiomas

Typically, these tumors present as painless and insidious progressive monocular loss of vision.

! Note

The initially fluctuating course of visual loss can be misinterpreted as a sign of optic neuritis. Beware the diagnosis of atypical optic neuritis.

Occasionally these tumors cause no initial changes in the appearance of the optic disc, other than slow atrophy. More frequently, however, one sees small vessel hyperemia and tissue swelling on the surface of the optic disc that looks like mild papilledema. Later changes are caused by chronically elevated retinal venous pressure with shunting of retinal venous blood into the peripapillary choroid through optociliary shunt vessels (■ Fig. 12.1 b) that arise in 14 to 33% of cases. CT scanning detects these tumors easily, since they usually contain significant deposits of calcium. Bilateral tumors are also not uncommon.

Treatment of Optic Nerve Sheath Meningiomas

Treatment depends on the extent of visual loss and the distribution of the tumor in the posterior orbit. The more that these parameters indicate an unfavorable prognosis, the more that radiotherapy is to be preferred, since primary surgical excision of the tumor invariably damages the perineural pial vessels of the optic nerve, causing an ischemic infarction. This is the expected outcome, whether or not the tumor is successfully removed.

If visual loss is extensive, or the eye is completely blind, and/or there is contraindication to radiotherapy or if the mass is threatening to invade the chiasm, tumor excision, including amputation of the optic nerve, can help to minimize secondary orbital problems, such as progressive proptosis. For tumors that have already involved the chiasm, surgery is an unacceptable risk to the patient's remaining vision, and radiotherapy is the only treatment option, other than nonintervention.

Tuberculum Sellae Meningiomas

Meningiomas often arise in the suprasellar region. Typically, they cause a rounded elevation of the planum sphenoidale. Less commonly, there can be an associated hyperprolactinemia and/or hypopituitarism (both being late developments). Growth of these masses is usually asymmetric, causing an initially monocular, fluctuating loss of vision with a central scotoma, and frequently an anterior junction syndrome of the chiasm (see Chap. 3). Tuberculum sellae meningiomas constitute 3 to 10% of all intracranial meningiomas, and are first diagnosed in the patient's fourth to sixth decade of life. Women are affected much more (up to 90%) than are men.

Current practice is surgical excision, although complete extirpation is not often achieved. This is particularly true of those tumors having the *en plaque* pattern of growth. Consequently, recurrences are common (up to 50%), and the frequency of recurrence is proportional to the area of dura that has been resected. CT scanning effectively detects the extent and location of bony involvement, while MRI scanning is necessary for the differential diagnosis of pituitary adenomas and for studying the precise relationships between the tumor and neighboring vessels, and the extent of intracanalicular involvement. The most common misdiagnosis of tuberculum sellae meningiomas is recurrent optic neuritis.

Clinoid and Sphenoid Wing Meningiomas

Twenty-five percent of all meningiomas arise near the anterior clinoid processes or along the sphenoid wings. Most affected are women (66%) aged 30 to 50 years. Exophthalmos is caused in 50% of cases, and optic disc swelling occurs (often bilaterally) in half of all meningiomas of this category. Growth through the superior orbital fissure and into the orbit is common, and is usually associated with prominent hyperostosis of the sphenoid wing, as seen on CT scans. Typical visual field findings include:

1. An ipsilateral central scotoma.
2. A unilateral hemianopic defect.
3. A homonymous hemianopia (caused by tract damage).

Most of these tumors can be surgically debulked to the extent that compression of the optic nerves and/or chiasm is relieved. The closer the tumor is to the midline, the more likely that its removal will be incomplete and the more likely that complications will be encountered. Tumors close to the sphenoid midline often extend to the contralateral side, which can require successive operative procedures on one side, and then the other. Stereotactic radiotherapy for these tumors is considered an attractive alternative, given the high rate of complications and postoperative neural

deficits that can be expected with surgical approaches to meningiomas on the skull base.

Conclusion

Visual symptoms are often the first indication of a brain tumor. They must be detected and correctly identified so that appropriate treatment can be quickly started. Following surgical and/or radiotherapeutic treatment, regular ophthalmic monitoring is necessary, to detect early signs of recurrent growth.

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Chapter 13

Central Disturbances of Vision

J. Zihl, U. Schiefer and J. Schiller

The fifth Marquis of Salisbury – briefly a prime minister of Great Britain – noticed at a court ceremony a young man who gave him a friendly smile. "Who is this young man?" he whispered to his neighbor. "Your eldest son!" answered the latter . . .
Lord David Cecil: Description of a Prosopagnosia; Damasio et al., in:
Oliver Sacks: *The Man Who Mistook His Wife for a Hat*

A central disturbance of vision should be suspected when an ophthalmic examination finds normal visual acuity and normal appearing anterior and posterior segments in both eyes, in the setting of a plausible complaint of difficulty with recognition of visual images. The human visual system does not terminate at the primary visual cortex. On the contrary, central processing of images begins at the striate cortex. Given the well-vascularized tissue of the poststriate visual cortex, damage to vision in these regions is comparatively uncommon (found in approximately 2% of cases of posterior brain disease) and is often transient, managing to recover within a few weeks following onset. It is all the more important to recognize the significance of transient loss of central visual function, as it often occurs as an ischemic prodrome of subsequent permanent infarction with irreversible loss of visual perception. In contradistinction to most disturbances of the posterior visual pathways, in which there is a deficit of vision, central disturbances are

see also Video 11.3

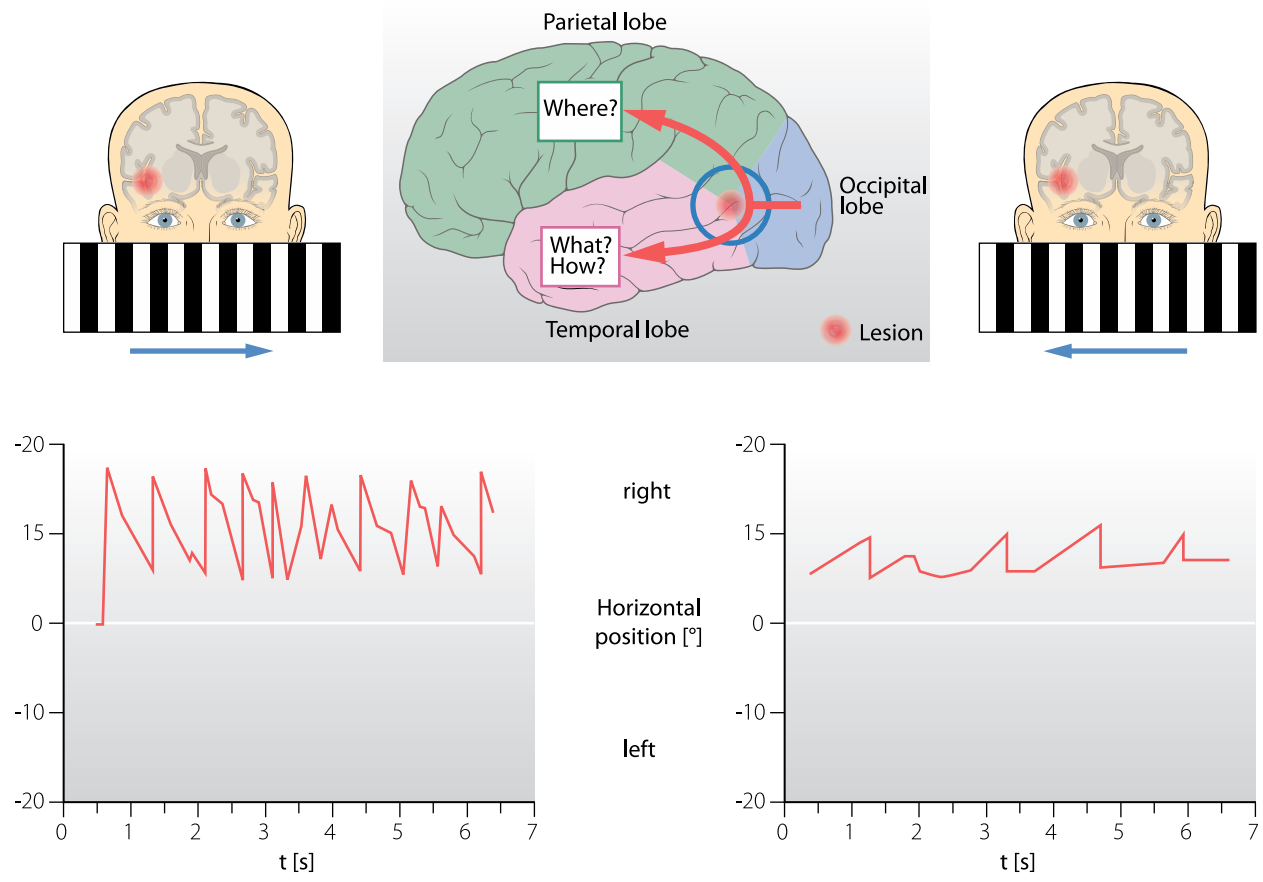


Fig. 13.1. The "where and what" system: a schematic diagram of afferent pathway connections with ramifications in the occipitoparietotemporal transitional zones. The effect of a (usually broad) lesion in this area on optokinetic (OKN) responses: patterned stimulus movement toward the side of the lesion is associated with a loss of or reduction in OKN responses, as compared with stimulus movement in the opposite direction, or away from the affected side. This is described as an OKN asymmetry

just as likely to be accompanied by an "excess" of visual perception. Many patients find it difficult to describe the changes to their vision well enough to allow proper recognition of the nature of their visual loss. This chapter provides an overview of important signs, symptoms, and simple investigational methods for analysis of such cases. In addition, appropriate diagnostic and therapeutic measures are discussed.

Topographic Organization of Visual Perception

Recent research results suggest a regional functional specialization of poststriate visual cortical areas. Analysis and representation of visual information take place in differing cortical regions, between which there is an active interchange of information.

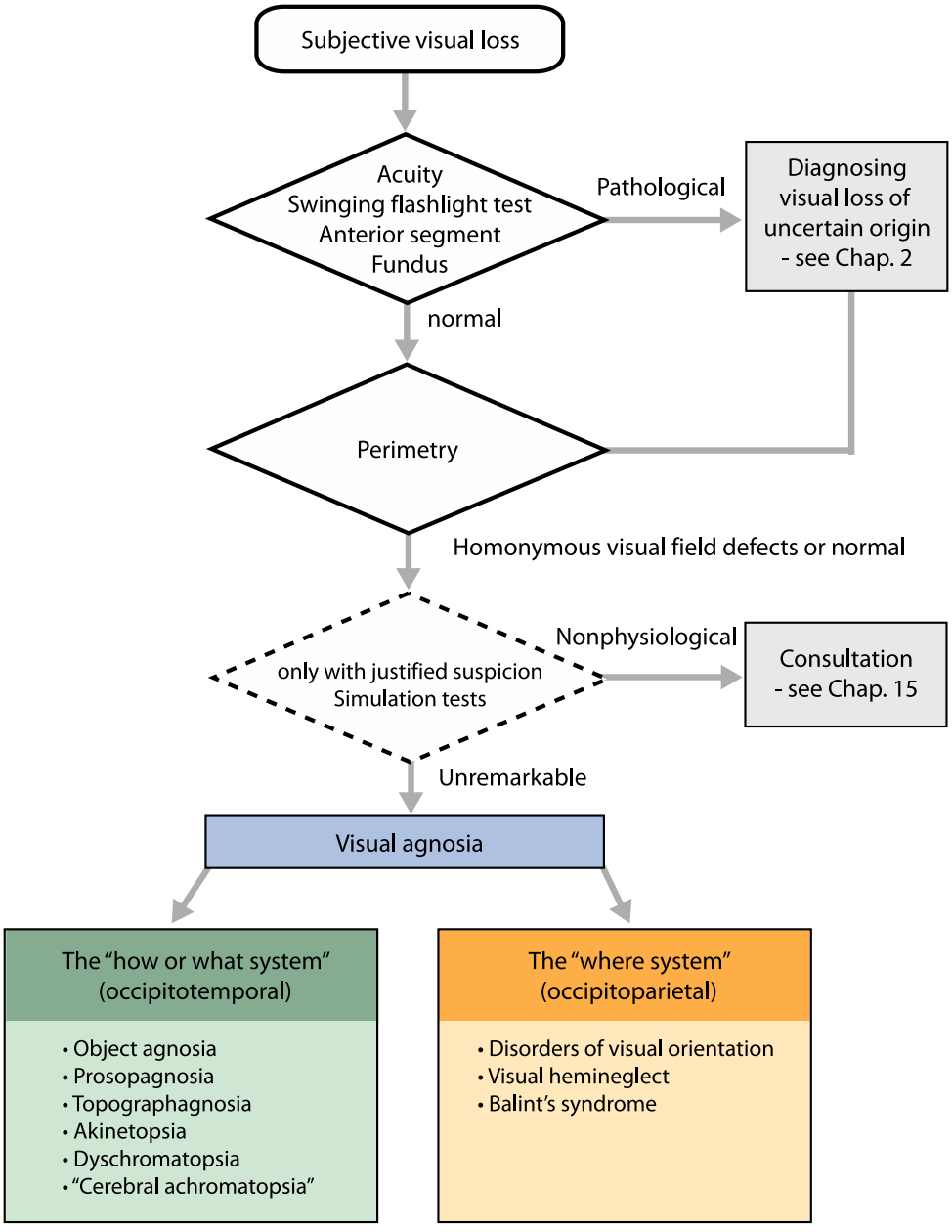
Pearl

Occipitotemporal areas are important for the perception and recognition of colors, objects, and faces (the "how or what system"), while occipitoparietal areas are more closely associated with visual spatial perception and orientation (the "where system") (■ Fig. 13.1).

However, isolated loss of individual elements of visual perception, such as color, movement, spatial perception, or facial recognition, is unusual if not rare. More commonly, there is a combined loss of higher visual functions.

Symptoms of Central Visual Disturbances

The symptoms of central visual disturbances depend on the location of disease or injury (■ Table 13.1). Damage to the retrogeniculate visual pathways or the primary visual cor-



Flow diagram. Diagnostic procedures in the case of suspected central disturbances of vision

Table 13.1. Summary of commonly described symptoms in central visual disturbances

Symptoms	Visual Disturbance/Diagnosis
Location of damage: posterior visual pathways, primary visual cortex	
Failure to notice objects or persons; narrowing of field of view; collisions with obstacles	Homonymous visual field defects, visual neglect, Balint's syndrome
Reading problems (locating the beginning of a line of print)	Homonymous paracentral visual field defect to the left
Reading problems (locating the end of a line of print)	Homonymous paracentral visual field defect to the right
"Blurred vision"	Loss of: acuity, spatial contrast sensitivity, fusion, accommodation
Increased sensitivity to light	(central) disturbance of light adaptation
Increased need for light	(central) disturbance of dark adaptation
Visual agnosias	
Location of damage: occipitotemporal "how or what system"	
Confusion/misperception of faces	Prosopagnosia
Confusion/misperception of objects	Object agnosia
Disturbed perception of moving objects	Akinetopsia
Confusion/misperception of places, paths; problems with map reading	Topographagnosia
Colors indistinct; confusion of similar shades of color	Dyschromatopsia
Colors darkened; scene appears gray or of monotonic brightness.	Cerebral achromatopsia (which should be distinctly separated from hereditary, or congenital achromatopsia)
Location of damage: occipitoparietal "where system"	
Loss of orientation in familiar surroundings	Disturbance of visual orientation, most often associated with a visual field defect
Neglect of the left half of space or of the left half of a body of text	Visual (hemi)neglect
Bilateral disturbance of attention	bilateral visual neglect (Balint's syndrome)

tex is characterized by homonymous visual field loss, as well as impairment of basic visual functions, such as visual adaptation, spatial contrast perception, accommodation, and binocular fusion.

Visual Agnosias

Definition

Visual agnosias are disturbances of visual recognition of objects, faces, places, paths, or letters, caused by lesions of higher visual centers located in parietotemporal and occipitotemporal cortical visual areas or their associated subcortical connections.

Sigmund Freud, as one of the first to describe this clinical phenomenon, spoke of failure of assembly of a sensation into a whole.

Neglect/Hemineglect

Definition

Neglect refers to a failure of visual attention – visual stimuli in the hemifield contralateral to the lesion are ignored, a condition referred to as **hemineglect syndrome**.

In most cases, there is damage to the nondominant (right) cerebral hemisphere. This disturbance of perception occurs most often in the left visual hemifield, and fortunately in many instances, tends to regress during the first few months after acute onset of the damage. It can occur with or without accompanying homonymous visual field defects. The patient with hemineglect sees no need for compensatory or explorative eye movements to the left, since for him/her the affected side of visual space simply does not exist. Diagnostically, this condition is often characterized by the so-called

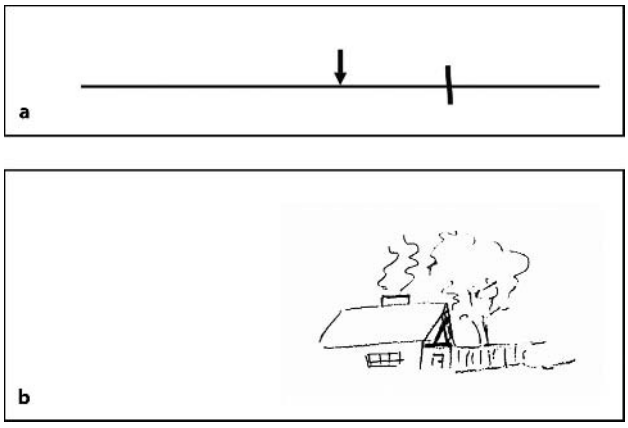


Fig. 13.2. Visual (usually left-sided) hemineglect. **a** Displacement of the subjective center toward the right in the line-bisection test; the *arrow* indicates the correct center. **b** Drawing from memory. Note the displacement of the image toward the *right-hand side* of the drawing area, as well as the missing elements in the *left-hand portions* of the drawing

Table 13.2. Diagnostic tests to be used in cases for which there is a suspected loss of central visual function

Suspicion of:	Diagnostic tests
Homonymous visual field defect	Perimetry Confrontation tests: Finger perimetry (see Chap. 4) Ask: "How does my face appear to you? Is it complete?" Ask patient to read a short passage of text aloud.
Diminished acuity	See diagram of diagnostic strategies in Chap. 2
Disturbance of color perception	Pseudoisochromatic plates (e.g., Ishihara) Presentation of large, colored objects in various portions of the visual field Naming of colored objects
Disturbance of stereopsis	Titmus test Random dot tests (Lang, TNO test)
Visual agnosia	Visual recognition of objects (real objects, pictures)
Visual (hemi)neglect	Line bisection test (■ Fig. 13.2 a) Drawing from memory (■ Fig. 13.2 b) Confrontation testing: with successive stimulus presentation in the right or left hemifield the stimulus is detected, while with simultaneous presentation of the stimulus in both hemifields the left hand stimulus is ignored (extinction phenomenon)

extinction phenomenon: When both hemifields are simultaneously stimulated, the stimulus in the (usually) left hemifield is ignored, while temporally successive or consecutive stimuli in the two hemifields can be correctly detected. Additional diagnostic tests include line bisection, in which the center of a line is displaced away from the neglected side, and drawing of familiar objects from memory, in which the left hand portions of objects are omitted (■ Fig. 13.2 b and ■ Table 13.2). Balint's syndrome, found in company with bilaterally symmetrical parietal lobe disease, produces severe impairment of vision best understood as a bilateral form of visual neglect. Patients with this visual disturbance have a marked compression or narrowing of their field of visual attention, and – despite a retained visual field – can perceive only a small portion of their surroundings. Often perception is limited to a single object or a small portion thereof. In addition, these patients have difficulty with volitional movement of gaze direction and cannot comply with requests to look toward objects presented outside their narrowed field of perception. The consequences include marked deficits in field of view, loss of visual orientation, and reading deficits.

Hallucinations

Definition

Hallucinations are deceptive perceptions for which there are no underlying adequate stimuli. With pseudohallucinations, the affected individual – in contradistinction to true hallucinations – is aware of the deceptive nature of the perception.

Hallucinations appear to result from a failure of visual reference or suppression functions, whereby patients are confronted with distorted or exaggerated visual impressions (■ Fig. 13.3). If the visual experience is limited to perception of abstract figures or colors, the hallucinations are referred to as simple, and the disease is most often found in or close to the primary visual cortex. If the images consist of objects or even a depiction of a sequence of events, they are described as complex hallucinations, and the diseased areas of the brain are found in the higher visual (poststriate) cortex.

Pearl

Complex hallucinations can be volitionally suppressed by saccadic eye movements. Patients should be specifically asked about this when complex hallucinations are suspected.

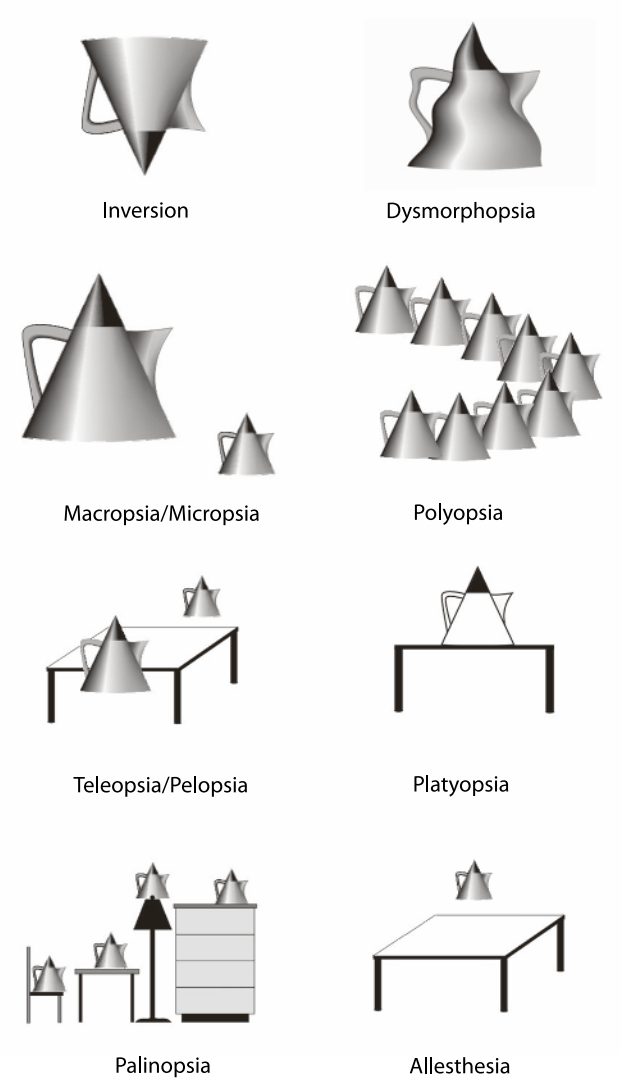


Fig. 13.3. Schematic diagram of the most common (pseudo) hallucinations. Upside down: inverted objects. Macropsia/micropsia: objects seen as too large or small. Telopsia/pelopsia: objects seen as too far or near. Palinopsia: objects seen in "correct relation" to others (e.g., exclusively situated on horizontal planes) and thus in multiple locations (a subtype of polyopsia). Metamorphopsia: objects misshapen. Polyopsia: multiple images of a single object (a failure of the "extinguishing center"). Platyopsia: loss of spatial perception in which all objects appear flat. Allesthesia: objects appear to be floating

Visual (pseudo)hallucinations are much more common than visual agnosias or visual hemineglect. Specific questioning about pseudohallucinations will often elicit a positive response, especially in patients with migraine and visual aura. A particularly pronounced form of pseudohallucination occurs in the so-called Charles Bonnet syndrome, named after the Swiss naturalist who first described it. Patients with advanced visual loss, as in age-related macular degeneration, can experience hallucinations in the blind areas of their central visual field. Neural activity in higher visual centers becomes independent of input through the usual afferent pathways, and can lead to the recall of complex visual memories of past scenes and events that seem to fill in the missing areas of vision. History taking from these patients requires tact. Many are reluctant to describe their experiences, or fear that the images are a sign of impending madness. An explanation of the source of the problem can provide them with wonderful relief.

Visual Illusions

Definition

Visual illusions are deceptive perceptions for which visual stimuli are adequate, but are then misinterpreted (incorrectly processed).

■ Figure 13.4 gives a summary of the highly varied appearances that visual illusions can form.

An important feature is the temporal latency of several seconds or minutes, separating the illusion from the inciting event. This is an important differentiating criterion for illusions of retinal origin, as in the persistence of immediate afterimages following a dazzling light exposure.

A completely accurate differentiation of these perceptual disturbances is not always possible. For example, in patients with the metamorphopsias of migraine, one should not refer to pseudohallucinations, but rather to pseudoillusions, since these usually have an inciting visual stimulus.

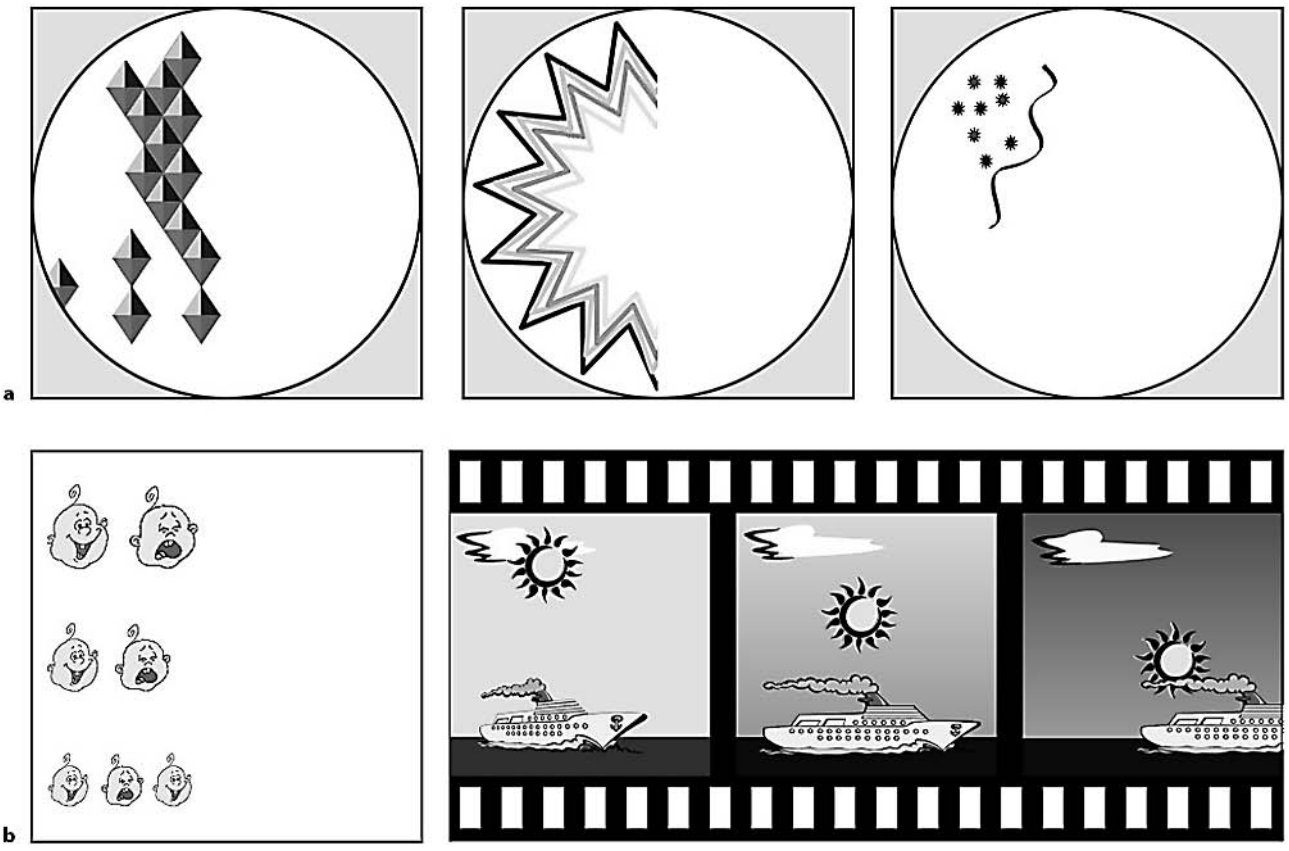


Fig. 13.4. Schematic diagram of the most common illusions (after Kölmel 1988). **a** Simple visual (pseudo)hallucinations/illusions are characterized by comparatively small but disruptive visual elements; these can appear unformed or alternatively as filigreed or finely structured objects. **b** Complex visual (pseudo)hallucinations/illusions by contrast are marked by perceptions of faces, complex scenes, or sequences of events

Diagnosis of Central Visual Disturbances

History/Techniques of Interview

Patients with acquired brain damage are often not able to provide a clear description of their visual problems. Often they report in general terms that they have poor vision or that they have lost vision in one eye. Not infrequently, they ascribe their problems (collisions, reading difficulties) entirely to their environment. They say, for example, "People are impolite and won't allow me to pass by", or "Everything is dark", or "I can't understand what I read". Their descriptions are often characterized by anxiety and fear: fear of public places, of getting lost, of being seen as demented. They are often aware that they can no longer properly read, and that they see colored spots, snakes, or animals when no such things are actually there. They may say that they are "imagining things" or they report that everything appears dull or dark. Through systematic questioning, useful information can be gleaned. The questions should be indirect in nature, focused not so much on the visual disturbances per se, but on their consequences, i.e., on the effects that they have on the patients' observations and experiences (■ Tables 13.1 and 13.3).

Anton's Syndrome (Visual Anosognosia)

Definition

The inability to recognize one's own illness is described as an anosognosia. When patients completely deny visual problems, though they have obviously and severely impaired vision (**visual anosognosia**), it is referred to as **Anton's syndrome**; this can be produced by a parietotemporal lesion in the right cerebral hemisphere.

Table 13.3. Catalog of questions for when a central disturbance of vision is suspected

Have you noticed any change in your vision since the time you became sick?
Is your vision not as clear as it used to be?
Are you having problems avoiding or bumping into people or obstacles? Do people or objects suddenly appear from out of nowhere?
Are you having problems with reading? When yes: • Are letters missing at the beginnings or ends of words? • Are you having problems with finding the beginnings or ends of lines of print? • Are you having problems with losing the line that you are reading?
Are you being dazzled by bright lights more frequently than before?
Do you have the feeling that you need more light than before? Does everything appear to be too dark?
Do colors now appear to be washed out, brighter than usual, unusual, or strange?
Have you seen colored patterns, stars, spots of light, lines, fogging or other unusual images during or since the time you became sick? When yes: • On which side?

Symptom-Guided Diagnostic Tests

Using the information obtained from a carefully taken history, simple symptom-guided diagnostic tests can be used in the office to establish an initial differential diagnosis (■ Table 13.2).

Pearl

When testing visual recognition, one should make certain that the patient does not touch the objects or use any nonvisual sense (e.g., hearing or smell). In addition, the visually determined naming of objects should be specific and not rely on circumlocutions, such as "It's used for writing", rather than "pencil".

Additional Tests

Specific Diagnostic Tests

A complete neuro-ophthalmic examination is first necessary to eliminate ocular sources of such problems as refractive polyopsia, metamorphopsia, impairment of contrast sensitivity, and photophobia (Chap. 2). The fundus appearance will give valuable clues to the presence of vascular, neoplastic, or inflammatory changes affecting the health of the retina and/or optic nerve.

Pearl

Any suspicion of a central visual disturbance makes careful visual field testing mandatory. In addition, reading fluency must be tested, as it is most likely to be impaired by parafoveal homonymous field defects

Widespread lesions affecting the occipitoparietotemporal boundary region – the transitional zone between the "where system" and the "what system" (flow diagram; ■ Fig. 13.1; ■ Table 13.1) – produce the clinical phenomenon of an asymmetry in optokinetic nystagmus (OKN). A patterned stimulus moving horizontally toward the diseased side of the brain will fail to produce a normal train of saccadic movements (counter to the direction of the pattern movement), when compared with the response to stimulus movement in the opposite direction. This asymmetry of OKN responses is best elicited by ensuring an equal rate of movement, when comparing OKN responses with right- versus left-moving patterns (Chap. 11).

Pearl

Since directional descriptions of OKN often lead to confusion, it is best to record the results of testing by noting *the side of the patient toward which the moving stimulus has produced abnormal responses.*

Modern neuroimaging procedures (CT and MRI) can often determine the location and the cause of disturbances of central vision (Chap. 20). Since other neurological deficits are frequently associated with central visual disturbances, a more complete neurological examination is always necessary (Chap. 21). Patients with posterior brain damage can also have impairment of visual attention, of visual and verbal memory, and/or of language (anomia, aphasia). Thus,

disease located in this region is practically always an indication for referral to a neuropsychologist. Neuropsychology is primarily focused on the study of disturbances of higher visual functions (spatial perception, object perception, reading, visual recognition, maintenance of visual attention or retention of visual information in memory).

Therapeutic Options

Pearl

Fortunately, many patients with posterior visual pathway disease show some spontaneous improvement in visual function within the first few months after onset.

For cases of homonymous visual field loss, which is the most frequent visual disturbance in this group of patients, there are neurorehabilitation or occupational therapy facilities associated with many neurology/neuropsychology departments. These facilities commonly have programs that include clinically tested methods for maximizing the prospects for recovery following brain damage. These include oculomotor compensation strategies for improvement of field of view, visual exploration, visual orientation, and reading. This can result in a significant reduction in functional visual impairment after 20 to 30 lessons over a period of just 2 to 3 weeks. Other methods, such as visual stimulation in the transitional zone between damaged and intact regions of the visual field, remain controversial. Unfortunately, well-intentioned efforts to instruct patients in methods that might compensate for visual field defects (by using head turning, or tilting the head to one side or the other) have not been clinically successful.

Counseling

There should be an initial counseling session immediately following the first office examination, to explain to the patient as clearly as possible the cause for his or her visual difficulties. At the same time, there should be a discussion of the realistic chances for spontaneous improvement in visual function, and the physician should also use this opportunity to clarify the reasons for referral to other specialists and the anticipated diagnostic testing that will likely follow. More complete explanation and counseling should follow completion of all relevant diagnostic examinations. A systematic discussion of all available options for management will reduce the patient's sense of insecurity without raising false or exaggerated expectations.

Pearl

Where possible, the patient's closest relatives should be included in these discussions, as they too need to understand the potential risks to the patient (e.g., in driving) associated with visual field loss or hemineglect.

It is especially important for patients with paracentral loss of visual field caused by posterior pathway disease to be warned in the presence of others (preferably close family members) that this type of visual loss makes safe driving impossible.

If the visual loss persists for a period of 3 months, discussions with the patient and relatives or close advisers should be directed toward a long-term plan for appropriate changes in occupational and social aspects of daily living. In this regard, referral to an occupational rehabilitation program may be most helpful.

Conclusion

Due to their unusual disturbances of vision, many patients with central visual damage will first seek the care of an ophthalmologist. This chapter is meant to provide a basis for systematic investigation and characterization of such visual disorders. Appropriate diagnostic and therapeutic care of such patients requires a multidisciplinary approach, including participation by neurologists, neuroradiologists, neuropsychologists, and neuro-ophthalmologists. Whenever a central disturbance of vision is associated with progressive symptoms (which may include sensory loss, oculomotor paralysis, or altered levels of consciousness), an immediate investigation should begin, including neuroimaging and neurological examination.

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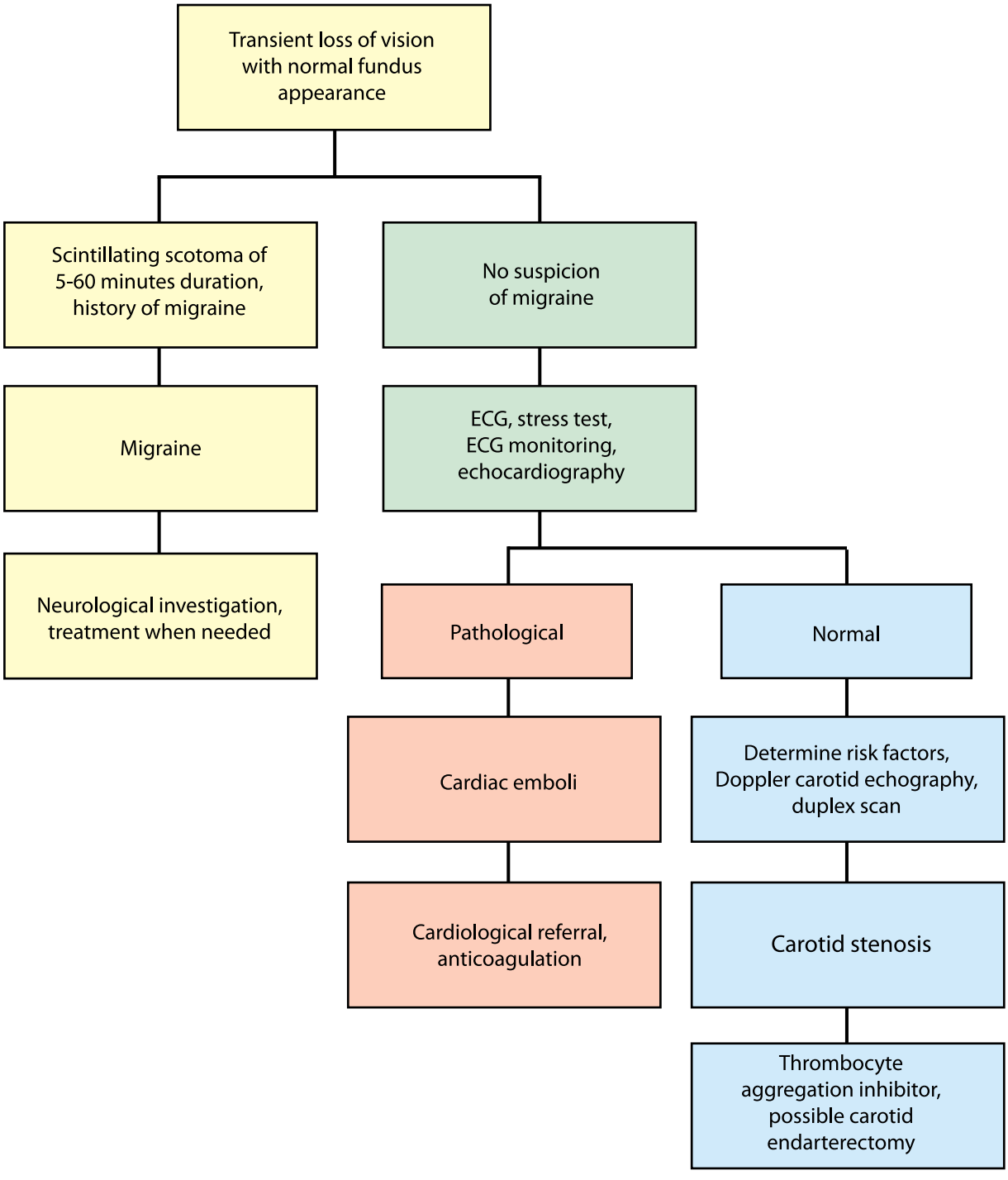
Chapter 14

Transient Visual Loss

H. Wilhelm

By **transient visual loss** we mean a drop in visual acuity or a loss of visual field, analogous to the transient ischemic attacks (TIAs) of neurological disease that last no longer than 24 h. This chapter does not discuss transient visual loss for which primary ophthalmic disorders are evident, such as intermittent angle closure glaucoma, vitreous clouding, retinal venous stasis, or the transient obscurations found in papilledema. Patients complaining of transient loss of vision frequently cause clinicians a great deal of worry, since the nature of their problem is often obscure. They may describe dramatic symptoms of visual loss without there being even a trace of objectively verifiable pathology. This can naturally lead the physician to consider a wide range of disorders, leading to a complex series of diagnostic tests, often without significant findings. Since a transient visual disturbance can be the harbinger of a retinal arterial occlusion, or even a stroke, the physician does not have the option of just giving up.

Amaurosis fugax is often used as a synonym for transient visual loss, but this is not completely correct. The problem is seldom expressed as periods of true amaurosis. Indeed, there are instances in which an excess of visual images obliterates portions of the visual field, such as in the scintillating scotomas of migraine.



Flow diagram. Sequence of diagnostic testing in the work up of suspected central nervous system causes of transient visual loss

Pathophysiology

Initially, the diagnostician must rely on the history provided by the patient, but before he/she can form a diagnostic opinion, he/she needs an understanding of the pathophysiologic mechanisms involved. With the exception of rare epileptic conditions that affect central visual centers, ischemic disturbances are ordinarily the principal cause of transient visual loss. The source of ischemia in turn can be vasospasm, focal vascular disorders, thromboses, emboli arising from larger vessels or the heart, general circulatory deficits (as in cardiac pump failure or circulatory collapse), and problems of blood composition, such as polycythemia and hyperviscosity syndromes.

These pathogenic mechanisms can in turn have multiple different sources, requiring a variety of different diagnostic considerations. A dilatative cardiomyopathy in a patient on the waiting list for a heart transplant can, in principle, cause the same visual disturbance as can a bout of faulty circulatory regulation in a competitive athlete. Patients often suffer from multiple disorders, e.g., cardiac arrhythmia combined with carotid stenosis, or migraine and erythrocytosis. The cause of the problem in a particular case can be reliably determined only by adhering to a disciplined approach during the diagnostic workup.

A Pragmatic Approach to Identifying the Cause

History

It can be difficult to determine whether one is dealing with a monocular or a binocular complaint, for patients frequently describe a homonymous visual field defect as monocular. If portions of a binocular image are described as missing, one is probably dealing with a homonymous loss, since monocular field loss is ordinarily compensated by the preserved field in the unaffected eye. When flickering lights are reported, one should ask about the abruptness of onset of the visual loss. Retinal ischemia tends to occur hyperacutely.

When a young patient describes a scintillating scotoma and has no apparent risk factors for vascular disease, questioning can be focused on symptoms likely to occur in migraine. If the patient has significant risk factors for vascular disease, for instance in a young patient with type I diabetes, one can direct questioning toward other symptoms that characterize ischemic disease.

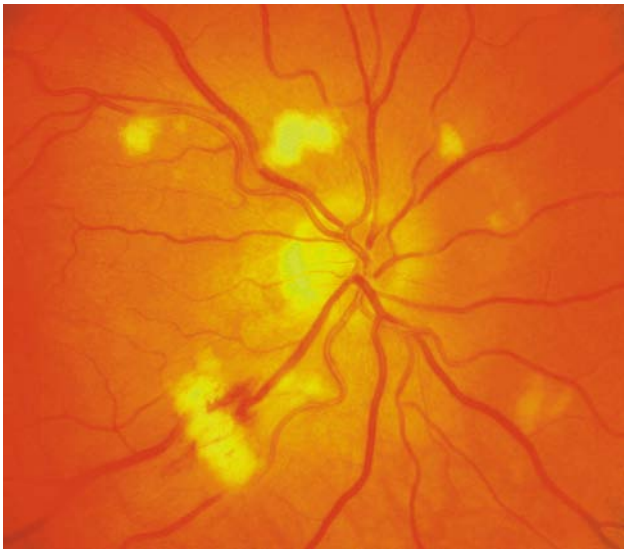


Fig. 14.1. Multiple retinal surface infarcts (cotton-wool spots) in a 58-year-old patient with an abdominal tumor and an associated hypercoagulopathy

Migraine

Migraine visual aura is probably the most frequent cause of transient visual loss, and the scintillating scotoma is the most common type of visual defect in transient disease. Patients with migraine typically describe a sequence in which a small central spot gradually spreads out into the peripheral field with a lateral convexity, a zigzag, shimmering (often-colored) border zone, and a trailing, central visual field defect (see ■ Fig. 16.1) that gradually fades away. These auras can last for 5 to 60 min, but are more commonly 10- to 30-min long. Their duration can vary from one episode to the next, and the patient usually has an established prior history of migraine. When such a scotoma appears without an ensuing headache, the diagnosis of migraine can be accepted only if the patient has a prior history of migraine (see Chap. 16). Migraine need not be strictly unilateral.

Occasionally, and difficult to differentiate from vascular disease, is ocular migraine, in which the aura reflects a transient reduction in retinal, rather than cortical, blood supply. In this case, the complaint will be strictly monocular. Ocular migraine ordinarily does not produce scintillating scotomas, and frequently occurs without an ensuing headache. Only the stereotypical duration suggests the etiology.

One should avoid the term eye migraine, which is rather ambiguous, and which can confuse the distinctions between migraine with pain in or around the eye, painless visual auras, and ocular migraine with its transient reduction in retinal arterial blood flow.

Vascular Occlusions

If the patient does not report a scintillating scotoma and there is no prior history of migraine, vascular disease is the next category to suspect. One should ask about other signs and symptoms of vascular disease, in particular for a history of TIAs. A TIA is defined (*vide supra*) as a reversible loss of neural function that lasts for less than 24 h. Accordingly, amaurosis fugax is a form of TIA. It may seem unlikely that a source of emboli in the heart or the carotid artery can produce visual symptoms alone, without also causing somatic sensory or paralytic effects. However, there are good reasons for this phenomenon:

1. Visual symptoms are more striking than are transient changes in motor function or in somatosensory perception.
2. Due to the limited functional redundancy of the topographically organized visual system, even small insults can result in symptoms that rise to the level of conscious awareness.
3. The retinal blood supply is poorly collateralized, and the primary visual cortex lies in part within a watershed zone of vascular perfusion.
4. Laminar flow favors the blood supply to the visual system; hence, emboli are more likely to find their way into the system.

During history taking, the classical risk factors to be considered include hypertension, diabetes mellitus, hypercholesterolemia, and tobacco use. In addition, one should inquire whether there have been any prior cardiac events, including myocardial infarction, arrhythmia, murmur, prosthetic valve, myo- or endocarditis, or symptoms of heart failure. Review of a patient's medications will often reveal more about vascular disease than the patient can.

During initial contact with the patient, one should take notice of any indications of a potentially emergent problem. Fever, malaise, and/or lethargy in a younger patient may suggest an endocarditis or vasculitis, while in older patients one must consider the possibility of giant cell arteritic syndrome. If an injury or a chiropractic manipulation preceded the visual loss or if the loss was accompanied by onset of a severe neck/head pain, or signs of Horner's syndrome, a carotid dissection should be considered.

Diagnostic Workup When Migraine Is the Suspected Cause of Transient Visual Loss

When migraine is the suspected cause of transient visual loss, a complete neurological examination is appropriate. If there are any pathological findings on fundus or perimetric examinations, the diagnosis of migraine as the sole cause of transient visual loss should be questioned, and diagnostic imaging should be considered.

Diagnostic Workup When Embolic Disease Is the Suspected Cause of Transient Visual Loss

Ophthalmic Examination

Visual acuity, pupillary light responses, and perimetry are of central importance when embolic disease is suspected. The anterior segment of each eye should be examined, looking for evidence of chronic ischemia. Anterior chamber flare, (initial) unilateral reduction of intraocular pressure, iris neovascularization and secondary glaucoma are important signs.

Fundus examination should focus on evidence of vascular disease:

1. Are there signs of hypertension, vascular narrowing, or cotton-wool spots?
2. Are there signs of vascular sheathing that suggest vasculitis, venous stasis, or chronic ischemia?
3. Is the optic disc pale, or does it have blurred margins, edema, or surface hemorrhages or cotton-wool spots to indicate an ischemic optic neuropathy?
4. Are there vascular changes to suggest a systemic disease, such as diabetes mellitus, leukemia, or endocarditis?

One should search carefully for emboli in the retinal vessels. This may be the *only* positive fundus finding with no other clue as to the source of the problem. In cases of recent embolization of the retinal arterioles, very small particles may be found in the most peripheral vessels only. Acute embolization of the central retinal vessels by cholesterol emboli is often followed by disintegration and dispersal of the particles into the periphery, as has been reported by several observers.

Aside from very rare tumor and/or fat emboli, there are three types of embolic particles:

1. Cholesterol emboli are a glistening gold to light-yellow color, tend to lodge at arteriolar bifurcations, and are easily broken up and dislodged into more peripheral vessels, as can sometimes be induced by anterior chamber paracentesis. They often originate from eroding plaques in the carotid arteries or in the aortic arch (■ Fig. 14.2).
2. Fibrin thrombocytic emboli are matte gray in color, occlude longer segments of retinal arterial vessels, and can mimic the appearance of a string of pearls. They arise most commonly from the carotids, the aorta, or the heart. In patients with coagulopathic disorders, they can appear de novo (■ Fig. 14.3).

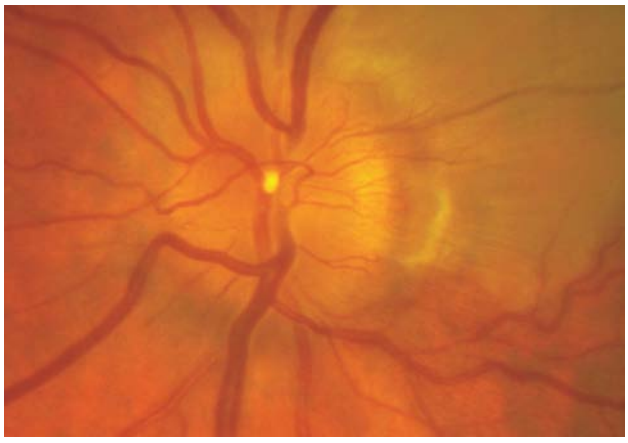


Fig. 14.2 Cholesterol embolus lodged in an arterial bifurcation in a 65-year-old patient with abrupt onset of a visual field defect

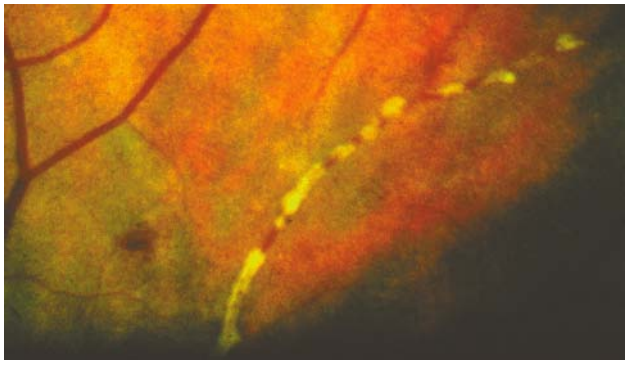


Fig. 14.3 Enlarged fundus photograph of a chain of fibrin/thrombocyte emboli in a retinal arteriole

3. Calcified emboli arise predominantly from the heart, are large and round, do not glisten like the cholesterol particles, usually stop at vascular bifurcations, and seldom move into the peripheral arterioles.

Pearl

The patient's complaint often gives an important clue as to where one should look when searching for an embolus. If the area of visual loss is seen in the superotemporal quadrant of the visual field, for instance, the search should concentrate on the inferonasal fundus.

Perimetry will reveal whether any permanent damage has been done, or whether the occlusions were short lived and reversible, with only a temporary reduction in vision.

Additional Diagnostic Tests

Angiography

Carotid Doppler ultrasonography and B-scan echography of the major arteries supplying the brain (duplex scan, ■ Fig. 14.4) have largely replaced other diagnostic methods, such as ophthalmodynamometry or ocular plethysmography and related techniques. These are nonetheless simple, reliable, and noninvasive. Cerebral angiography is seldom necessary in the workup of microembolic disease. Magnetic resonance angiography (MRA) is a suitable and noninvasive procedure that images the large arteries of the neck and skull base in their entirety. It is particularly suited to the diagnosis of dissecting carotid aneurysms.

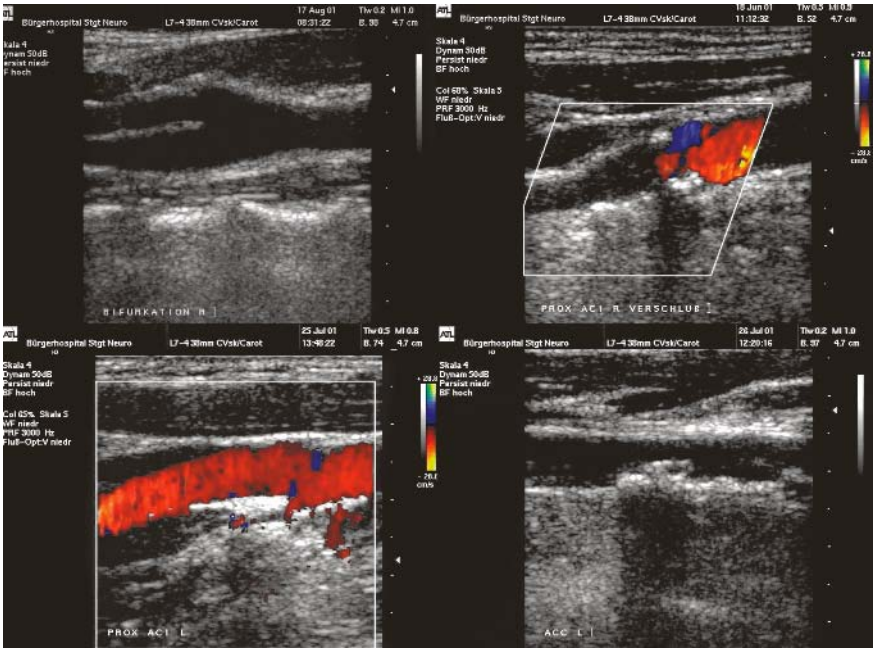


Fig. 14.4 Typical carotid ultrasound findings. On the *left side* are normal scans of the carotid bifurcation (*top left*) and the internal carotid artery (*bottom left*). On the *right side* is an occlusion of the internal carotid artery (*top right*) and an ulcerated plaque with acoustic shadowing (*bottom right*)

Cardiovascular Testing

Cardiac stress testing, echocardiography, transesophageal echography, and 24-h ECG monitoring provide a more complete picture of a patient's cardiovascular condition. The use of these tests has not been as traditionally common as has the use of carotid Doppler scanning, but they can reveal systemic vascular diseases that commonly lead to transient visual loss. If there is reason to suspect greater problems with vascular disease than the patient is aware of, prompt referral for a cardiovascular evaluation is very important.

Pearl

Perhaps the first test to be done – before the initial encounter is done – is for the ophthalmologist to feel the radial pulse. An irregular pulse, as in atrial fibrillation, or a tachycardia may provide a ready clue as to the source of the visual symptom.

Internal Medical Evaluation and Laboratory Testing

In those patients for whom a migrainous syndrome has been ruled out, a number of important risk factors should be investigated:

- Tobacco use
- Arterial hypertension
- Diabetes mellitus
- Hyperlipidemia

In addition, signs and symptoms of other systemic disorders should be investigated, and the younger the patient, the more urgent the investigation should be. There may be clues to less common collagen vascular diseases, such as arthritis, serositis, Raynaud's phenomenon, xerostomia, sicca syndrome, or alopecia. Pregnancy, postpartum status, estrogen and/or progesterone use (as in oral birth control pills), and dehydration can all increase the likelihood of transient visual loss. One must also remember to consider systemic vasculitic syndromes, such as giant cell arteritis in elderly patients (check the erythrocyte sedimentation rate), panarteritis nodosa in patients of all ages, and Takayasu's arteritis in the young. Sarcoidosis and Behçet's disease can present with vasculitic symptoms and transient visual loss. If there is any suspicion of these disorders, consultation with an experienced internist or rheumatologist is indicated. Further, though even less common than are vasculitic syndromes, heredofamilial disorders of coagulation can lead to thrombotic episodes and transient bouts of visual loss. As a rule, these are more likely to cause venous thromboses, but have also been known to present with arteriolar occlusions. ■ Table 14.1 lists the relevant hereditary disorders.

Table 14.1. Hereditary coagulopathies, *PAI* plasminogen activator inhibitor, *t-PA* tissue-plasminogen activator

Disorder	Prevalence
Factor V resistance to activated protein C (Factor V Leiden)	2–7%
Protein C deficiency	0.1–0.5%
Protein S deficiency	0.003%
Antithrombin III deficiency	0.1–0.5%
Fibrinolytic disorders: Factor XII, plasminogen, PAI, t-PA deficiency (difficult to detect)	
Prothrombin 620210A mutation	

Among acquired vasculitic disorders, antiphospholipid syndrome, and hyperhomocystinemia should be considered. Antiphospholipid syndrome gives rise to arterial and venous cerebral thromboses. As a rule, hematologic screening for thrombophilia will either rule out or indicate this potential source of disease. A high level of risk for ischemic disease can arise from several combinations of heredofamilial disorders and other risk factors. Factor V resistance to activated protein C has a prevalence of about 5%. Looking for such cases and reducing the risk of thrombotic events by starting appropriate prophylactic therapy (such as folic acid to treat hyperhomocystinemia) is particularly important when no other risk factors are present, when the patient is young, or when there is a family history of frequent thrombotic events.

A few malignant tumors can also give rise to an elevated risk of thromboses. These paraneoplastic syndromes should be considered when no other source of an ocular ischemic syndrome can be found (■ Fig. 14.1). Pregnancy and the use of oral contraceptives likewise increase the risk of thrombotic events.

Transient Visual Loss in Various Clinical Syndromes

Carotid Stenosis

The transient visual loss associated with carotid stenoses are for the most part short, not lasting for more than 15 min. The use of the term fugax is nonetheless legitimate. The diagnosis can be made by carotid Doppler ultrasound testing. The degree of stenosis determines the subsequent steps to be taken. When there is complete carotid occlusion or the location of a stenosis is not surgically accessible,

reduction of modifiable risk factors (chiefly cessation of tobacco use) and daily use of aspirin are the only available options. The same applies to those stenoses that are less than 70%. If the stenosis is above 70%, an endarterectomy should be considered.

A patient with transient monocular loss of vision caused by ischemic disease has a significantly elevated risk of suffering a stroke or a retinal infarction.

The height of this risk cannot be known precisely, as the results of individual studies have been as variable as the expression of ischemic disease. It can be concluded that patients with transient visual loss who are under 40 years of age and have normal carotid blood flow have a annual risk of stroke of about 3%. Endarterectomy reduces this risk of stroke significantly, despite the considerable risk of surgery. Such patients should be evaluated in a consulting vascular service, where the alternate risks of medical and surgical management can be explained to them carefully.

In all cases the use of thrombocytic aggregation inhibitors – classically aspirin – is advisable. When aspirin is contraindicated or not tolerated, alternate use of clopidogrel 75 g daily can be recommended. The ideal dose of aspirin has not been precisely determined, with study recommendations varying from 50 to 1,500 mg daily. Current practice tends toward the use of lower doses, with 81 mg of enteric-coated preparations being the most common.

Cardiac Disease

Atrial Fibrillation

Cardiac sources of cerebral and ocular ischemia are manifold and varied. Atrial fibrillation is the most important, in that the risk of stroke in patients over 60 years of age is increased fivefold. Detection of the problem is as simple as remembering to check the radial pulse for the characteristic irregularity of ventricular contraction. Anticoagulation by dicumarol or warfarin reduces the risk of stroke considerably.

Mitral Stenosis or Prosthesis

Mitral stenosis after rheumatic fever results in a high risk of cardiogenic emboli, and is often coupled with atrial fibrillation. Following valve replacement, the risk remains high, and there is little difference in risk comparing mechanical or bioprosthetic valves.

Endocarditis

Another important clinical syndrome is that of bacterial endocarditis. These patients present with fever, shaking chills, and night sweats. Fundus examination reveals dot and blot hemorrhages and so-called Roth spots, which appear as flame-shaped retinal hemorrhages, each having a white exudate at the center. In those with acute onset endocarditis, *Staphylococcus aureus* is the most common infectious agent, while subacute disease is most frequently found to be associated with *Streptococcus viridians*. These patients need immediate admission to hospital for treatment with intravenous antibiotics. The same applies to patients with chronic wasting diseases or long-term immunosuppression, which can likewise lead to bacterial endocarditis.

Mitral Valve Prolapse

A common disorder, mitral valve prolapse is usually asymptomatic. Still, there is an increased risk of cerebral or ocular episodes of TIAs. At a minimum, symptomatic patients need prophylactic treatment with agents that inhibit thrombocyte aggregation (e.g., aspirin or clopidogrel).

Various Additional Cardiac Causes of Transient Visual Loss

Other less common cardiac causes of transient visual loss include calcified aortic stenosis, myocardial infarction, atrial myxoma, and cardiac myopathy. Therapy in each of these cardiac diseases is different, but is usually more successful than the treatment of carotid stenosis.

Conclusion

Identification of the cause of transient visual loss requires a careful plan of evaluation by a knowledgeable ophthalmologist. Benign disorders, such as migraine, must be differentiated from more serious disorders that pose a greater threat to the patient's vision, such as stroke or myocardial infarction. The presence of risk factors, such as a coagulopathy and/or a vasculitic disease; an abnormal carotid Doppler ultrasound; and abnormalities found in cardiac testing are the foundations of a properly organized approach to the diagnosis and treatment of transient visual loss.

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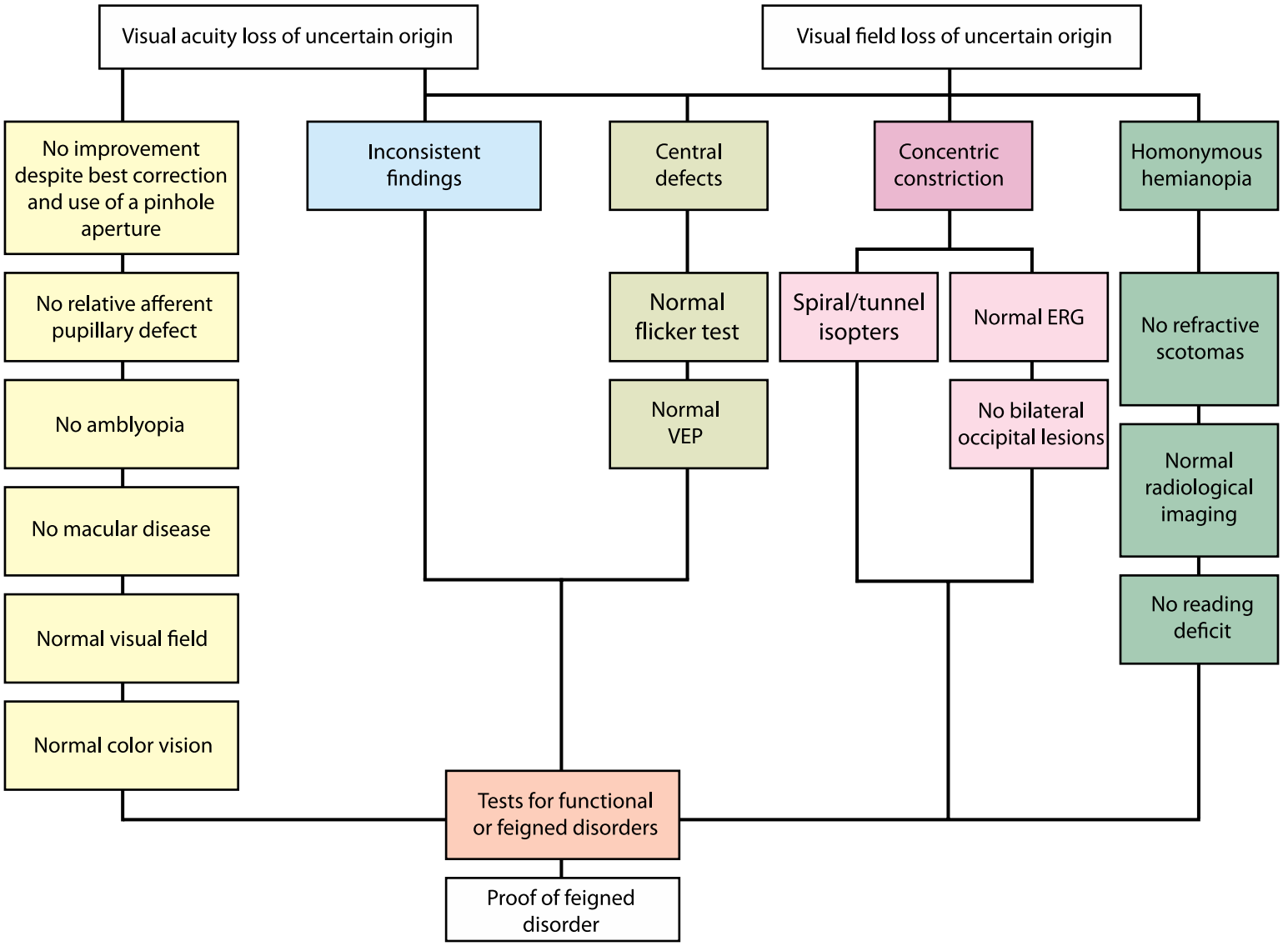
Chapter 15

Functional Visual Loss and Malingering

S. Trauzettel-Klosinski

Malingering is an intentionally deceptive mimicry of a nonexistent disorder, and **augmentation** is an intentionally exaggerated account of an existing disorder. **Functional visual loss** is a subjectively described visual disorder without an objectively observed abnormality. It is an unconscious, often subconscious, simulation of a nonexistent disease. (Synonyms include psychogenic visual loss, conversion, and hysterical visual loss). The related group of psychogenic ocular disorders includes functional disease, psychosomatic disease, and artificial eye diseases. Psychosomatic eye disease is initiated by a psychically triggered (or heavily influenced) organic disease with demonstrable pathological findings, as for example, in some reported cases of glaucoma, uveitis, or central serous retinopathy. Artificial eye diseases arise by self-inflicted trauma (autoaggression) and have demonstrable pathological findings during the eye examination. This type is usually associated with psychoses or so-called specific personality disorders. Simulation and functional visual disturbances are characterized by a tendency to mask themselves. The specific diagnosis is important, however, so that the patient will not be unjustly classified as a simulator on the one hand, and on the other hand, to spare the patient with functional disease any unnecessary and expensive tests, to avoid the development of additional symptoms, and to provide the patient with appropriate help. This chapter covers the clinical presentation, the differential diagnosis, and the specific ophthalmic diagnosis of these disorders. The most important principles are addressed here, although a more complete description and extensive bibliography are provided in Trauzettel-Klosinski (see Trauzettel-Klosinski [1997a, b] under "Further Reading").



Flow diagram. Test sequence for the differential diagnosis of a visual disturbance without a morphological correlate (modified from Trauzettel-Klosinski S [1997] Untersuchungsstrategien bei Simulation und funktionellen Sehstörungen. Klin Monatsbl Augenheilkd 211: 73–83)

Examination Strategies for Functional Visual Loss and Malingering

Although functional visual loss and malingering have very different origins and therefore require very different therapeutic measures, they produce identical clinical appearances and can be unmasked by the same methods. The term "malingering test" is used in the following sections as a generic term for the investigational strategies to be used in cases of feigned visual loss, independent of the disorder's cause.

Differential Diagnosis

It is not usually the patient's behavior, but rather a poorly described visual complaint with no apparent morphological correlate, that first suggests a nonorganic disorder. First, organic ocular and visual disorders that can present without related physical findings must be specifically ruled out of the differential diagnosis (■ Table 15.1).

! Note

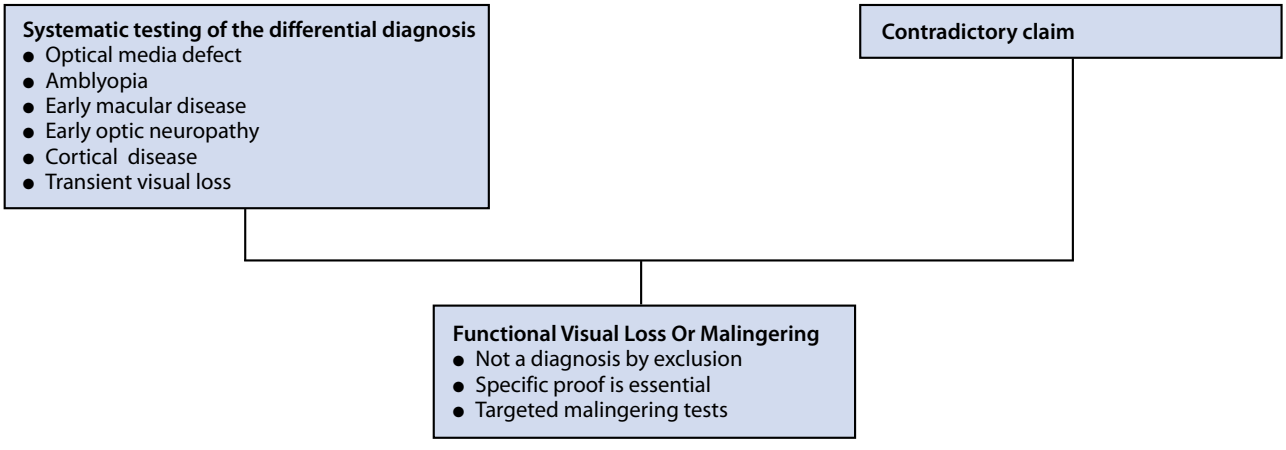
The diagnosis of functional or simulated visual loss cannot be made purely as a diagnosis of exclusion. A positive finding is required. Specific malingering tests must be used in the differential diagnosis.

Visual impairment of unknown cause without morphological correlates should cause the examiner to begin a systematic examination process that will clarify the diagnosis (see the accompanying flow diagram and Chap. 2). If poor visual acuity is not improved by use of the best spectacle correction or a pinhole aperture, the problem is not an optical one. If monocular visual loss is not accompanied by an associated relative afferent pupillary defect, there is no optic neuropathy. If there is no amblyopia (stereopsis, no strabismus, no anisometropia, central fixation), there are no signs of macular disease (fundoscopy, perimetry, fluorescein angiography, foveal fixation), and there is a normal visual field and color vision is normal, then suspicion of a feigned visual disturbance should initiate a series of malingering tests.

In many instances, suspicion is raised during the initial stages of the examination based on contradictory findings. One can then turn directly to a sequence of malingering tests. Unusual visual field defects should lead to a quick assessment of their reproducibility. In cases of a central scotoma, normal pupillary light reactions, unremarkable visually evoked potentials (VEP), or normal results on flicker testing as described by Aulhorn will effectively rule out a retrobulbar optic neuritis with a high level of certainty, see Trauzettel-Klosinski (1989) and Chap. 8. Concentric visual field constriction with a cylindrical or tubular profile (constant size of field at all distances from the eye), or spiraling isopters found during kinetic perimetry, strongly suggests a nonorganic disturbance. The same applies to constriction of the visual field coupled with normal electroretinography (ERG) responses and no signs of bilateral occipital disease.

Feigned hemianopic visual field defects are occasionally encountered. Suspicion is aroused when no pathology is found on CT or MRI scans (often brought in by the patient from recent prior evaluations), also when homonymous hemianopia is not accompanied by reading problems (see below and Chap. 24). Other differential diagnostic considerations may be suggested when a patient complains of transient visual loss and then yields varying results during repeated examinations. Such patients are sometimes mistakenly categorized as malingerers. For this reason, it is especially important to clarify the nature and the source of the problem, saving the physician time wasted and the patient unjust accusations.

Table 15.1. Visual loss with no apparent morphological correlate: Hidden disease? Functional disorder? Malingering?



Pearl

In contradistinction to overt malingering, patients with transient disturbances of vision may report no problem during the time of the examination, and give only an after-the-fact, historical account of their symptoms.

A carefully collected history of the duration, type, and inciting factors of the episodes will yield necessary information. Frequently encountered symptom groupings, for example, include those of transient ischemic attacks associated with carotid stenosis or migraine, transient obscurations with papilledema, circulatory insufficiency with vasospasm, and the neural conduction delay of Uhthoff's phenomenon (for details see Chap. 14).

General Principles of Testing Strategy

Before starting the malingering tests, the examiner should plan the strategy in detail, prepare the tests in advance, and then move quickly and efficiently through the sequence, to deprive the subject of the time needed to deceive. The strategy has three sections (■ Table 15.2).

Pearl

The strategy does not attempt to degrade the patient, but is rather a means to demonstrate the actual presence of vision where it is claimed to be absent.

Table 15.2. General principles of examination for when functional or feigned loss of vision is suspected

1. Testing for the reproducibility of responses
2. Examination methods • Testing of reflexes: such as pupillary light responses, optokinetic nystagmus • Deception: testing unrelated functions that the patient assumes are vision related • Measuring a single function with multiple methods: e.g. kinetic versus static perimetry • Objective tests: ERG, VEP
3. Establish proof

ERG Electroretinogram, *VEP* visually evoked potentials

Having established the intactness of function in those with functional visual loss, one can then carefully explain that the visual function in question is variable in nature and can be expected to improve at any time. When dealing with malingerers, exposure of and confrontation with the contradictions in their claims is advisable. When conducting a test for formal certification of vision, there is often a "recovery" at this juncture. The details of such testing are given at the end of this chapter.

Testing Principles for Claimed Impairment of Visual Acuity or Blindness

The choice of tests is determined by the extent and type of monocular or binocular visual loss (■ Table 15.3).

Table 15.3. Examination strategies for alleged blindness or loss of vision

Bilateral blindness	Monocular blindness or visual impairment	Bilateral visual impairment
1. Testing of reflexes • Observation of behavior • Blink reflex • Prisms: fixation movements • OKN • Mirror-induced pursuit movements • Fixation star of direct ophthalmoscope • Pupillary light reactions 2. Deception • Tasks of coordination that require no visual function • Saccades on command combined with index finger movements 3. Objective testing methods • VEP, ERG	1. Testing of reflexes • Pupillary reactions: relative afferent pupillary defect • Convergence test • Refixation movement when covering the healthy eye 2. Binocular Tests • Prisms • Stereoacuity • Confusion test (polarized tests, red–green glasses, etc.) 3. Testing central visual functions by other methods • Central thresholds at the perimeter • Preferential looking acuity • Fixation • Laser interferometry	1. Deception regarding the sizes of optotypes • Use of constant angular sizes of optotypes at varying distances • Testing with single optotypes, allowing no comparisons to other characters • Near acuities with optical magnification 2. Tests of central vision by other methods • Central threshold sensitivity at the perimeter • Preferential-looking acuity • Fixation • Laser interferometry • Probability of seeing 3. Objective methods • Acuity VEP • Multifocal ERG • OKN (quantitative) • Psychogalvanic reflexes

ERG electroretinogram, *VEP* visually evoked potentials, *OKN* optokinetic nystagmus

Feigned Binocular Blindness

Observations of Behavior and Triggering of Reflexes

For those complaining of complete blindness, behavioral observation provides telling information. When greeted for the first time, does the patient reach for your hand, bump into obstacles, or have trouble finding the examination chair? On passage down a flight of stairs, those with functional visual loss have a problem with each step, whereas those with organic blindness will indeed experience some uncertainty with the first step, but will be able to negotiate the rest of the flight without hesitation.

Pearl

In those with functional blindness, intactness of the following reflexes can be demonstrated: the blink reflex response to rapidly approaching objects, refixation movements in response to abrupt prism placement before an eye, and optokinetic nystagmus responses to a train of moving objects (a qualitative measure of reflex intactness).

A particularly effective test is the oculomotor response to movement of a mirror that is large enough to fill most of the field of view (■ Fig. 15.1). A large bathroom mirror (or similar type) that can be held in front of the eye(s) to be tested is slowly turned back and forth on a vertical or horizontal axis. Gazing into the moving mirror, the subject will see both distant and near objects appearing to move with equal angular velocity, which will elicit ocular pursuit movements when vision is intact. The stimulus to eye movement in the mirror test is especially strong and cannot be reliably suppressed.

Similarly, the fixation target or star figure in a direct ophthalmoscope, when projected onto the fovea, presents a stimulus to fixation that is very difficult to suppress.

Complete blindness caused by disease in the anterior (pregeniculate) afferent pathways will destroy the pupillary light reflexes, both direct and consensual. Accommodative convergence (the patient's own hand can be used as a proprioceptive stimulus) or squeezing attempts at lid closure against the examiners forcible grasp to hold the eyes open will elicit pupillary constriction, regardless of visual sensory intactness. Retrogeniculate disease will usually leave the pupillary light reflexes intact during clinical testing (Chap. 5).

Deception

Tasks of coordination that require no visual input, such as pointing to one's own body parts or bringing the index fingers together, will frequently be failed by those with functional blindness, while the organically blind have a robust sense of body position based on proprioception, and can perform these tasks with no effort. Another test is to provoke saccades first verbally ("left," "right"), and then only by index finger movements.

Objective Testing Methods for When Bilateral Blindness Is Alleged

The ERG and VEP tests are available as objective tests, when the above mentioned methods are not conclusive. Despite their objectivity, however, these tests are also subject to at least occasional false-negative results (see below).

Differential Diagnosis of Cortical Blindness

Cortical blindness or the loss of function in the primary visual cortex (area 17, V_1, or striate cortex), is marked by the complete absence of conscious visual perception, e.g., complete loss of the blink reflex. Optokinetic nystagmus cannot be elicited in affected adults. The pupillary reactions to light and accommodative convergence are retained; fundus appearance and ocular motility are normal. The VEP is not always clearly diagnostic, and its reliability in this setting is controversial.

The existence of blindsight, an extrastriate, unconscious visual perception, will be mentioned here only as a potential, selective, residual perception under particular conditions (e.g., motion perception), and not as a proof for testing claims of blindness. Additional neurological symptoms

Fig. 15.1. Mirror-induced ocular pursuit movements. The examiner turns a large mirror slowly back and forth in the horizontal direction, while the subject gazes at the reflected image. Both distant and near objects will appear to move with the same angular velocity, eliciting eye movements that the examiner can easily see. It is almost impossible for the subject with intact vision to suppress the movements, unless he/she can fix his/her gaze on some stationary object; hence, the use of a large mirror that fills the field of view as widely as possible. The examiner must take care to note that the subject is not looking intently at some stationary object outside the margin of the reflected image

Video 15.1

in company with cortical blindness may or may not be present (e.g., hemiplegia, somatosensory loss, aphasia, disorientation). Many of these patients tend to ignore their visual loss, a form of visual agnosia, also called Anton's syndrome. Lesions of extrastriate visual cortex (areas 18, 19, and higher cortical levels) do not produce blindness (meaning that visual reflexes can be elicited), but are associated with disturbances of visual recognition (e.g., loss of visual memory, alexia, or prosopagnosia), while visual perception remains intact. (Agnosias are covered in Chap. 13).

Alleged Monocular Blindness and Monocular Visual Impairment

Testing Visual Reflexes

Pupillary reflexes. With the swinging flashlight test (see Chap. 2), asymmetry in the afferent limb of the pupillary light responses can be demonstrated. A relative defect is present when the direct response falls below the consensual response. In cases of total unilateral visual loss, an amaurotic pupil shows no direct response to light, but retains an intact consensual response. The relative afferent pupillary defect (RAPD) is particularly important when dealing with monocular or highly asymmetric visual loss. Unilateral optic neuropathies, optic tract disease, chiasmal damage, and pregeniculate lesions are the usual causes of an RAPD. For diseases not affecting the afferent visual pathways, the swinging flashlight test is not usually helpful. This is true for example in cases of amblyopia. The swinging flashlight test will yield a normal result when obscuration of the refractive media is the cause of visual loss, except in cases of very dense vitreous hemorrhages.

When pupillary reflexes cannot be tested because of pharmacologic paresis, surgical distortion or inflammatory disease, binocular tests (see below) can be used.

Fixation reflexes. During cover testing, interrupting fixation of the healthy eye with an occluder will stimulate a refixation movement of the "bad" eye toward the object of regard.

Pearl

In cases of alleged monocular blindness, one can patch the "good eye" and then use the tests for bilateral blindness, as described above.

Binocular Tests

These are especially helpful, since one can often establish the actual visual acuity of the bad eye. There are the so-called confusion tests, because the subject being tested is not easily aware of which eye is contributing to the test results. More properly, truly binocular tests require the simultaneous contributions of both eyes, as in tests of stereoacuity and tests of responses to monocular prism introduction during binocular viewing. The relationship between stereoacuity and monocular acuity remains somewhat in dispute, but failure to detect stereopsis is in any event not very helpful. For example, subjects with poor development of stereopsis during childhood can have normal acuity in each eye, symmetrically alternating fixation, and no stereo vision at all.

Of the numerous confusion tests, only a few are given here. One can use polarizing filters, red–green glasses, or obscuration of the better eye, e.g., by progressive introduction of plus lenses during acuity testing, or when testing near vision with a plus lens before the better eye (only), sudden switching to reading distant optotypes with the "bad" eye. This will often yield a more accurate measure of acuity in the affected eye.

In the tests described by Fahle et al., computer-controlled presentation of optotypes with very short display times can be given in rapid binocular alternation, causing the test subject to lose track of which eye is being tested. However, such tests are likely to be used in referral centers only, and are not available in most practices.

Pearl

If during near tests of reading one quickly introduces a vertical opaque ruler over the nose, the nasal halves of each visual field will be obscured. In this case, both eyes are seeing monocularly, and no impairment of reading fluency will be demonstrated in subjects who have normal vision in both eyes. In patients with monocular organic disease, the ruler will disrupt their ability to read.

Alleged Binocular Loss of Visual Acuity

Proof of deception is most difficult to establish in this instance, since the partner eye cannot be used as a basis for comparison, and the remaining vision in each eye is usually good enough to prevent useful testing of reflex responses in binocular comparisons. Testing methods for this scenario rely on four basic principles.

Confusion of the Sizes of Optotypes Used in Acuity Testing

Size comparison of projected or charted optotypes that the patient is familiar with can be made more difficult when the examiner begins with the smallest available characters, or uses single optotypes in a random sequence of sizes. Instruments like the Freiburg acuity test, which determines spatial resolution thresholds on a monitor screen, allow the use of testing environments with which the patient is not likely to be familiar.

When measuring near acuity, one can use magnifying lenses with varying degrees of dioptric power: With increasingly plus lenses and with closer viewing distances, the higher the acuity should be, while with the addition of minus lenses and with increases in reading distance, the lower the acuity should be.

The Mojon chart displays optotypes, the contours of which are based on a shift between two lines (Vernier acuity). The visibility of the optotype is independent of its size, when the frequency of the lines is constant.

Pearl

By testing with a projected optotype of constant size at varying distances rather than varying sizes at a constant distance, the patient can be confused as to the angular size of the characters being used.

Probability of Seeing

When testing malingerers intent on deception, Gräf has used a series of Landolt rings with four possible openings (top, bottom, left, and right) and records 32 responses as to the number openings seen. Based on probability alone, guessing should yield eight characters correctly identified out of the 32 presentations. If only two or less presentations are correctly identified, it can be inferred that the patient is being willfully deceptive.

Testing of Central Vision by Other Methods

Testing of central vision by methods other than the usual varying angular sizes of optotypes presents the experienced test subject with an unfamiliar setting, which can yield informative results. Examples include the following:

- Central luminance threshold at the perimeter: Both the threshold of luminance increment perception and visual acuity fall in synchrony with increasing distances from the center of the visual field. The two measures remain closely related, independent of eccentricity. At a visual acuity of 20/20 (1.0), the central threshold of luminance increment perception will be 0.32 cd/m^2 (■ Fig. 15.2).
- Determination of grating acuity (preferential looking method)
- Testing of fixation maintenance with the target star of the direct ophthalmoscope or with a scanning laser ophthalmoscope. With the latter instrument one can use not only fixation targets of varying size, but the patient's fixation behavior can also be documented by video recordings.
- Determination of acuity by laser interferometry: One can measure the spatial resolution of the retina with an interferometer's stripe pattern, which is a completely unfamiliar method to most patients and which offers no basis for comparison with settings that are more familiar.

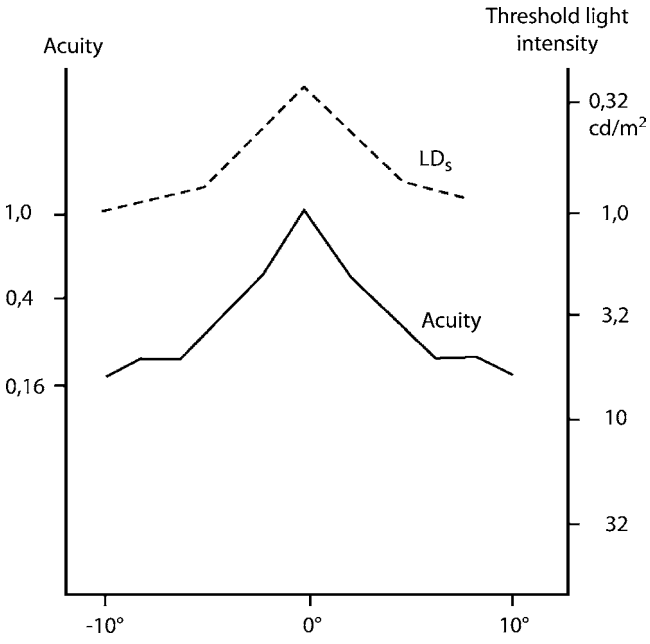


Fig. 15.2. Threshold luminance levels and visual acuity as a function of retinal location, as measured by the Tübingen manual perimeter (modified according to Aulhorn)

Objective Testing Methods for Alleged Bilateral Loss of Acuity

An objective determination of acuity is possible with use of a VEP method in which one measures the smallest angular subtense of a flickered checkerboard pattern that can produce a recordable cortical response. This can then be compared to a normative curve of acuities recorded by using normal subjects. This method is not entirely reliable, as the recorded potentials can be suppressed by the test subject (see below).

Optokinetic nystagmus can also be used as a quantitative method of acuity determination, either by recording the spatial frequency of the striped pattern that induces the nystagmus, or by determination of the angular size of a stationary fixation object needed to inhibit the nystagmus. The latter method has been improved with the use of an infrared nystagmography instrument that (except in the case of amblyopia) produces a good correlation between the resolution of the inhibiting fixation object and the level of spatial acuity.

When using objective methods, one should take care that the measurement is not influenced by poor cooperation, deficient fixation, or intentional accommodation.

Another objective method is the psychogalvanic response, a so-called lie detector. A few authors have used this technique to differentiate between malingering and

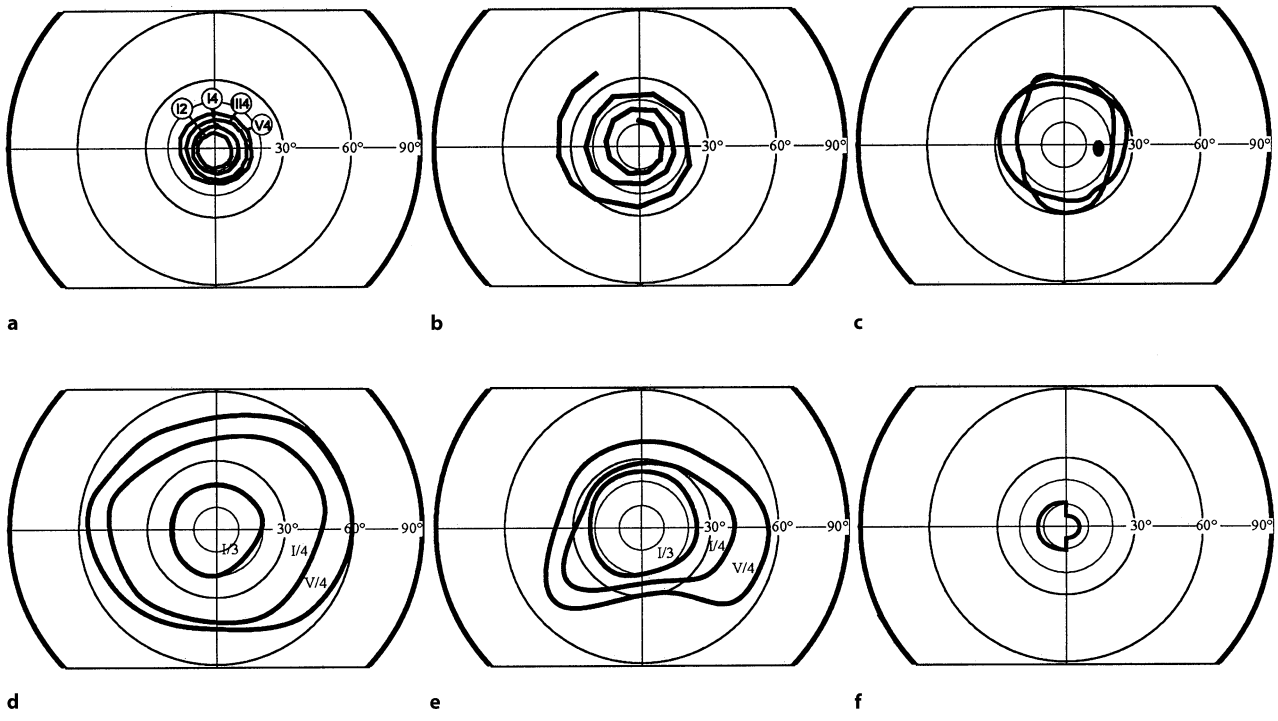


Fig. 15.3. The differential diagnosis of concentric constriction of the visual field. *Top* Typical configurations of the visual field in feigned loss of peripheral vision. **a** Symmetrical constriction of the more peripheral isopters (tunneling of the visual field). **b** Spiraling of isopters. **c** Crossing of adjacent isopters. *Bottom* Constriction of the visual field in cases of organic disease. **d** Symmetrical narrowing predominantly of the central isopters, caused by loss of media clarity. **e** Asymmetric constriction of the peripheral isopters in heredofamilial retinal degenerations. **f** Sharp discontinuities of isopters at the vertical midline and macular sparing in visual field loss caused by bilateral occipital lobe disease

functional loss of vision. Only among malingerers was the dermal galvanic resistance pathological, while patients with functional visual loss could not be distinguished from normal subjects.

Testing Strategies for Alleged Visual Field Defects

Alleged Concentric Constriction of the Visual Field

Nonphysiologic constriction of the visual field is usually marked by a symmetrical narrowing of the peripheral isopters in particular, so that they lie very close to the central isopters (■ Fig. 15.3 a). While this sort of finding is suspicious, proof of the falsity of the responses is needed, and as much as possible, determination of the actual isopter positions is necessary. The latter is especially important in cases of exaggeration with the intent to qualify for financial aid based on a visually disabled status, because such a status is usually defined by the isopter position for a particular peripheral test object, such as the Goldmann III4e.

A relatively symmetrical narrowing or depression of the predominantly central isopters (inside 30° of eccentricity) is usually attributable to media opacities or an age effect (■ Fig. 15.3 d). Tapetoretinal degenerations in their earliest phases often present with asymmetrical constriction of the more peripheral isopters (■ Fig.15.3 e). Marked constriction of all isopters with preservation of only 10 to 20° of visual field is often found in the later stages of the tapetoretinal degenerations. This presentation would be difficult to confuse with functional visual loss, since there is usually a prominent abnormality of the fundus appearance and the ERG will be extinguished. A central island of vision can often be found in the advanced stages of glaucomatous disc cupping. Less frequent cases of bilateral, sequential occipital cortical infarction can spare the macular representation of the visual fields, but this should be detectable by the presence of small discontinuities in some isopters at the vertical meridian, both above and below fixation, due to small asymmetries in the extent of damage between the two occipital lobes (■ Fig. 15.3 f).

Pearl

Strange configurations of constricted isopters, such as spiral shapes (■ Fig. 15.3 b), the crossing of isopters (■ Fig. 15.3 c), or other bizarre forms indicate a functional disturbance.

Testing Methods for When Concentric Constriction of the Visual Fields Is Suspected of Being Functional (■ Table 15.4)

Presence of Bizarre Alterations of the Visual Field

A normal visual field and one constricted by organic disease will have isopters that are evenly spaced, more or less, outlining the form of a cone with its peak at the center. On the contrary, functional disturbances usually cause the isopters to congregate closely with one another. This is variously referred to as tunnel or tubular constriction, since the cylindrical shape implied is fundamentally nonphysiologic. This is most conveniently investigated by old-fashioned tangent screen testing, done at distances of 1 and 2 m (■ Fig. 15.4). The position of an isopter is first marked on the black felt with white pins (making the response locations visible is helpful). Then the distance between the subject and the screen is doubled (from 1 to 2 m), and to maintain a constant angular size of the stimulus, it too is doubled in diameter. Testing will then show an identical result, rather than the physiologic expansion one would normally expect (the diameter of the isopter should double in size), thus marking the result as functional. This test is easily modified and can be adapted to a number of different testing environments.

Pearl

For monocular concentric visual field constriction binocular testing at the perimeter can be helpful. A genuine constriction to the level of 10° or less in one eye should preserve and allow demonstration of the physiologic blind spot of the other, unaffected eye.

Table 15.4. Test methods for when alleged visual field defects are suspect

Concentric constriction	Hemianopic visual field loss
One and two meter tangent screen testing	Binocular perimetry
Varying strategies of isopter testing	Tests of reading ability
Comparison of various perimetric methods (kinetic, static, automated threshold determination, video, microperimetry)	Hemifield stimulation Fusional vergence responses to prism-induced strabismus

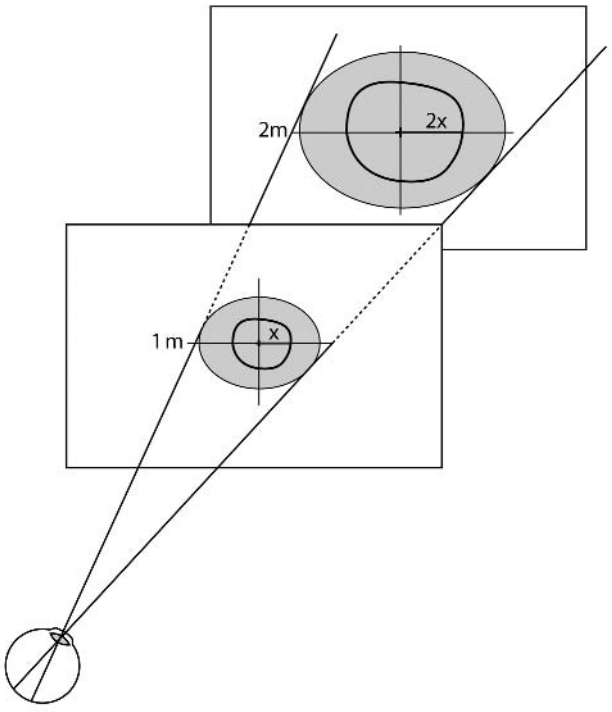


Fig. 15.4. Angular magnification of the visual field with increasing distance: With a doubling of the distance between the eye and the testing plane (usually a tangent screen), the diameter of an isopter will also double

Various Strategies for Isopter Testing

When testing bilateral concentric constriction of the visual fields, one can use a variety of strategies during isopter mapping with manual perimetric methods (e.g., with the conventional Goldmann or Tübingen perimeters):

- Repetition of stimulus presentations tests the reproducibility of response
- Moving the test objects from seeing to nonseeing areas (e.g., centrifugal motion from the center to the periphery), the subject can be asked to indicate the point of disappearance. Physiologically, the isopters thus recorded should lie only marginally outside the previously recorded locations.
- Changes in the sequence of test object presentation: reversing the conventional method of testing by using objects of lower stimulus values prior to using the larger or brighter test objects
- Determination of the true isopter location can be successfully confirmed with the following strategy, though only when the patient is not yet familiar with it: Initially, the patient is asked to fix attention on the fixation target. Later, the subject is told that to make the test easier, looking directly at the moving test object will be allowed. By observing fixation behavior, the spontaneous eye movements toward the test object can then

allow a more accurate estimate of the isopter's true location, confirming that vision is intact peripheral to the isopter recorded by conventional testing.

General Principles of Perimetry

Testing with alternate strategies, other than those described above, are very difficult for patients to compare. As general rule, when a visual defect appears on routine testing, it is usually helpful to test with another method. If the same result is obtained, the defect is much more likely to be a truly pathological defect. Other than conventional kinetic perimetry with the Goldmann or Tübingen perimeters, one can use threshold static perimetry (manual or as an automated grid), video screen devices or microperimetry using a scanning laser ophthalmoscope.

Testing Principles for Alleged Hemianopia

Binocular Perimetry

The most important method for testing alleged hemianopia is binocular perimetry:

- A true homonymous hemianopia will produce blindness to one half of visual space, and the physiologic blind spot will be detectable in the temporal seeing hemifield.
- True bitemporal hemianopia will show absence of the temporal half of the visual field in both eyes, i.e., the fields consist only of the nasal halves of the field; therefore the physiologic blind spots will not be detectable.
- True binasal hemianopias are very uncommon, but due to the absence of any overlapping binocular field, both physiologic blind spots and the peripheral temporal borders of the fields of both eyes will be detectable.

Additional Considerations

Reading ability. Homonymous hemianopias produce disturbances of reading, fluency, particularly when the field defects lie close to the center (see Chap. 24). Bitemporal and binasal hemianopias will have the same effect, but only in monocular viewing. Standardized reading texts can be used for testing.

The hemifield slide phenomenon. Binocular viewing in bitemporal or binasal hemianopias has no corresponding points of binocular vision, and all locations in the visual field are seen monocularly. This destroys the afferent pathway for fusional vergence reflexes. Since there is no motor control of binocular alignment, underlying heterophorias become manifest, e.g., a patient who had an antecedent exophoria will manifest an exotropia. Since the two visible hemifields are no longer linked to one another, separation, vertical displacement, and/or horizontal displacement of the remaining hemifields will frequently occur:

- Reading ability is impaired, and is particularly bad for reading tables of numbers.
- Vertical misalignment of the two hemifields will cause a vertical discontinuity during binocular viewing with one half of an object seen as higher or lower than the other.
- Exodeviation causes overlap of the nasal parts of the visual field with resulting diplopia. Esodeviation leads to a "gap" (see Chap. 2, ■ Fig. 2.3).
- Bitemporal hemianopias result in a postfixational blindness. When viewing objects that are relatively close, there will be an area of blindness that starts and expands beyond the object of regard.
- For alleged binasal or bitemporal hemianopias, placement of a prism before one eye will produce overlapping and doubling of images. Truly pathological defects will not allow any corrective movements, but those with functional disease will show intactness of fusional vergence movements to correct the prism-induced strabismus.

Pupillary deficits. Disease of the optic tract will always, and chiasmal disease will frequently be accompanied by a relative afferent pupillary defect.

Hemifield stimulation in functional homonymous hemifield loss. An isolated focus of disease in one side of visual cortex will show intact optokinetic nystagmus when the entire visual field is stimulated. Hemifield stimulation during optokinetic nystagmus or VEP testing will show detectable differences between the left and right hemifields when the loss is organic but not when it is functional.

Steps after Finishing the Malingering Tests

Once the malingering tests have been completed, the diagnosis of alleged visual loss should be clear, and the claimed loss of function should be either confirmed or denied.

Functional disturbances of vision occur most commonly in situations of conflict, inadequate support, excessive demands, or among those with suggestible or neurotic personality disorders. In a conflict situation the visual complaint will develop as a kind of appeal for help with symbolic content (can no longer see something or someone). The alleged loss has the effect of providing a compensatory gain: attention, care, considerate treatment. If the conflict is not resolved, the symptom may become permanently fixed or transferred to another organ (symptom shift, ■ Fig. 15.5). In this situation, the ophthalmologist is vested with an important responsibility, since he/she can differentiate clearly

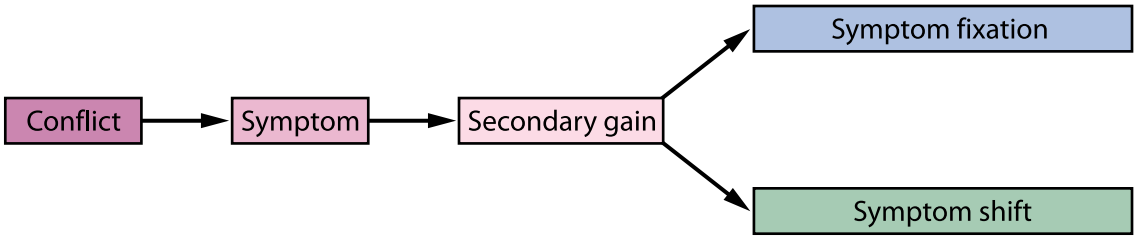


Fig. 15.5. The pathogenesis and psychodynamics of functional loss of vision (modified according to Trauzettel-Klosinski S, Klosinski G [1997] Psychogene Augenerkrankungen. In: Deter HC [ed] Angewandte Psychosomatik.Thieme, Stuttgart, pp 407–421)

between a functional visual loss and an organic disease. If sufficient time passes following the onset of functional visual loss, and it is shifted to a complaint of headache or abdominal pain, the physician then tasked with the patient's care will find it significantly more difficult, and often not definitively possible, to prove that the problem is a nonorganic disturbance.

On the other hand, a malingerer will have a specific desire or request: financial gain or protection from imprisonment, or the military draft. The individual's status as an opponent to, rather than as a partner with, the physician will become evident during the examination.

Steps to Be Taken When Malingering Is Proven

1. The malingerer should be confronted with the contradictions of his/her claims.
2. He/She should be made aware of the disadvantageous consequences of pursuing his claims, such as loss of insurability or license to drive.
3. To avoid a repetition of the claims, other physicians participating in his/her care should (consistent with proper confidentiality of the patient's records) be advised of the conclusions. In this regard, care should be taken that information about the patient's evaluation not be passed on without the patient's written consent. It is recommended that the malingering nature of the claim be clearly described, e.g., "contradictory claims" or "discrepancy between morphological and functional findings."
4. If the patient agrees to perform the tests properly and is in real need, a legally sanctioned method for the patient to receive assistance can often be found.

Steps to Be Taken When Functional Loss of Vision Is Proven

1. One should inform the patient that "fortunately," no organic disease is present.
2. One should try to discover the underlying causes through careful questioning.
3. For potentially solvable problems, such as excessive burdens experienced by students, one can offer practical assistance in having his/her work load reduced.
4. For problems whose sources are more difficult to identify, one can offer help with referral to a psychiatrist, to determine whether psychotherapy, medications, special testing, and/or crisis intervention are needed. This should be done with the purpose of avoiding fixation of the problem or transfer of the symptoms to another organ system.
5. Knowing the nature of the problem, other physicians involved in the patient's care can be spared the expenditure of time and expensive tests, as well as the risk of surgical intervention.
6. In every case, the patient must be given a face-saving pathway to retreat from the symptom complex. This can be as simple as an optimistic suggestion that a spontaneous recovery of function is just ahead, since there are no signs of disease. The suggestion can often be helped by the use of harmless but complex and time-consuming treatments, such as instillation of artificial tears according to precise directions as to the number of drops and the time of day at which they should be instilled. In addition, one can speak of the "beneficial effect" of a flash VEP.

Conclusion

With the methods described here, one can usually be successful in proving the functional nature of a visual complaint. The unambiguous diagnosis allows the institution of appropriate measures to help patients with functional loss of vision, and exposes the deception behind claims of visual loss in malingerers.

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Chapter 16

Headache from a Neuro-Ophthalmic Point of View

H. Wiethölter and H. Wilhelm

Headache is the most frequent cause for cooperative interaction between neurologists and ophthalmologists. Frequently, patients are seen first by their primary care physicians, and are then referred to ophthalmologists for further testing and management, chiefly to rule out ocular sources of pain. From there, they are commonly referred to neurologists, to be sure that something serious will not be missed. The diagnostic classification of headache is at first glance extraordinarily confusing or overwhelming, considering that the International Headache Society (IHS) has defined 176 different types of headache. This large number can be reduced to a more manageable level, since 90% of all primary headache syndromes are attributable to the two most common types, migraine and tension headache. The fact that there is no clearly defined system that allows for rapid classification of headache, especially cases of primary headache, underscores the importance of a carefully taken history and clinical examination.

Historical Clues When Evaluating Headache

A properly structured history will allow proper classification of 25% of all cases of headache. The most important elements of the history include the frequency, location, duration of episodes, intensity of pain, the course taken during episodes, instigating factors, and a family history of headache (■ Table 16.1).

Table 16.1. Checklist of history taking for a work up of headache

Frequency
Location
Duration of episodes
Intensity of pain
Usual course
Triggering factors
Family history

Frequency of Headaches

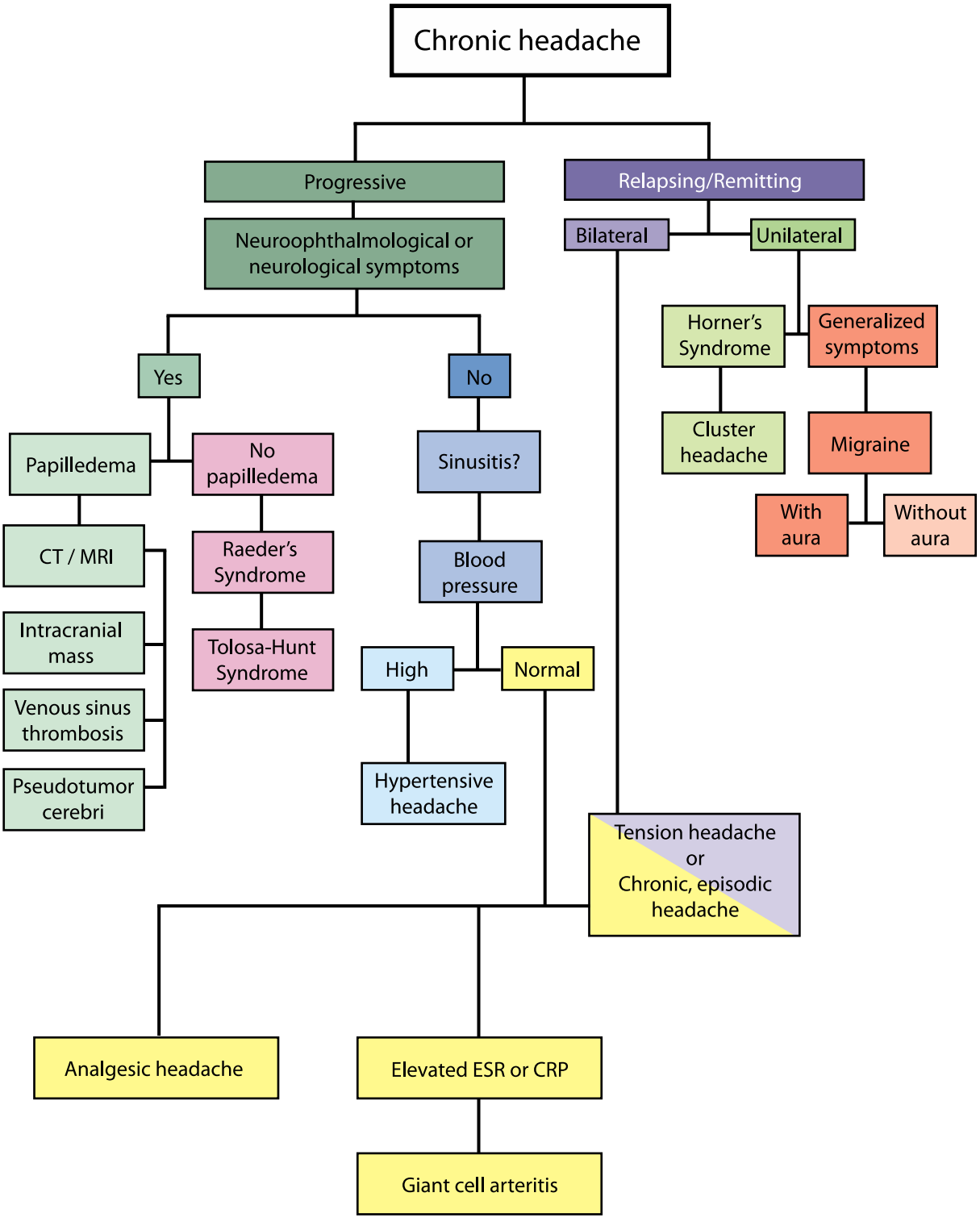
Throbbing headaches that occur once or twice a year or several times a month and which are accompanied by autonomic symptoms or signs are, generally, attributable to migraine. The episodic headaches of a cluster syndrome are usually confined to specific periods and often come in groups of up to several episodes each day. More frequent attacks of head and facial pain (up to 20 times daily) are caused by chronic paroxysmal hemicrania. The daily appearance of chronic headache is often the presenting manifestation of a tension headache or an analgesic-induced pain syndrome.

Localization of Headaches

Headaches can be strictly unilateral (as in cluster syndromes), predominantly unilateral (as in migraine), retrobulbar or retro-orbital (as in cluster syndromes), cervical with pain radiating into the occiput and parietal region (as in cervical neuralgia), or holocephalic (as in tension or analgesic-induced headache).

Duration of Episodes

The episodic pain of SUNCT syndrome (short-lasting unilateral neuralgiform headache with conjunctival injection and tearing) lasts for seconds, the paroxysmal hemicrania from 5 to 30 min, whereas the pain of cluster headaches lasts from 20 min to 2 h. Typical attacks of migraine headache can last from 4 to 72 h. Chronically persistent headache is found in those with tension headaches, analgesic-induced headaches, temporal arteritis, and pseudotumor cerebri.



Flow diagram. Diagnostic procedures for the workup of chronic headache

Intensity of Pain

The intensity of pain in headache syndromes is naturally highly subjective and differs substantially from one person to the next. The most intense pain is usually found in cluster headaches, migraine headaches, and paroxysmal hemicrania. Temporal arteritis causes a pain of intermediate intensity, while mild to intermediate levels of discomfort are associated with chronic tension headache. Venous sinus thrombosis commonly causes alternating phases of mild to intermediate pain.

Course of Pain

An intracranial hemorrhage can produce pain that starts precipitously and with full intensity in a stroke like fashion. Cluster headaches and chronic paroxysmal hemicrania develop within a few minutes. The pain of migraine attains its greatest intensity between 15 min and 2 h of duration. The pain of venous sinus thrombosis has a diurnal course with nocturnal and morning pain, aggravated by the horizontal position during sleep, and partially relieved by erect posture after arising.

! Note

A steadily progressive intensity of head pain in a patient with no prior history of headache suggests a serious cause, such as obstruction of the flow of cerebrospinal fluid (e.g., aqueductal compression), or elevated intracranial pressure (pseudotumor cerebri).

Triggering Factors and Family History

Some headaches have specific triggering factors. For migraine, these include alcohol, changes in the sleep–wake cycle (e.g., jet lag), hunger, hormonal changes (e.g., the menstrual cycle), states of stress or agitation, abrupt climate change, and withdrawal from the use of caffeine. Attacks of cluster headache can be triggered by alcohol or by vasodilating medications. There are no specific trigger factors for chronic paroxysmal hemicrania or for tension headaches.

● Pearl

In those with migraine, there is frequently a strongly positive family history, especially among primary relatives – parents and siblings.

Migraine

The most important disease that produces headache is migraine. The pain can arise with or without an antecedent aura. About 7% of men and 14% of women suffer from this malady.

⋮ Definition

Migraine is a unilateral, frontotemporally located, pulsating, or boring headache. It frequently appears on awakening and worsens with activity after arising. Due to the accompanying light and sound hypersensitivity (photophobia and phonophobia), patients are compelled to seek out rest, darkness, and silence. Associated autonomic phenomena include nausea and vomiting. Initiating trigger factors can be identified by 90% of sufferers. The pain lasts for 4 to 72 h and is commonly relieved by the following night of sleep. Attacks that last more than a day are uncommon.

The source of pain is thought to be a sterile inflammatory reaction within the perivascular tissues of meningeal vessels, induced by changes in the neuronal activity of a generator in the region of the brain stem nuclei. It is accompanied by the release of vasoactive preinflammatory substances (neuropeptides).

Initially, an aura is produced by a spreading wave of neuronal activity ("cortical spreading depression") that moves across the cerebral cortex. This in turn induces a change in cerebral perfusion. Experimental evidence has found that the volume flow of blood decreases in the occipital cortex, and the hypoperfusion then spreads like a wave at a rate of 2 to 3 mm/min in the direction of the frontal cortex. The release of proinflammatory substances that stimulate pain receptors is responsible for the associated pain.

Migraine with Aura

By nomenclature, migraine with aura (previously known as classic migraine, ophthalmic migraine, hemiparetic migraine, hemiplegic migraine, or complicated migraine) is distinguished from migraine without aura (previously known as simple migraine or hemicrania). The aura corresponds to a disturbance in the occipital cortex, or less commonly to disturbances within the brain stem. Affected patients describe the perception of lightning flashes, and fortification scotomas. The latter are shimmering, zigzag

Fig. 16.1. The most common visual aura of migraine appears as a unilateral (binocular) geometric zigzag figure that usually begins in the center of the visual field and gradually extends to the periphery over a period of 15 to 30 min. The aural images can be very bright and colorful. The term fortification scotoma is sometimes used to describe the figure, due to the similarity in appearance to the ground plan of a seventeenth century fortification

lines that start at the center of the visual field and gradually expand peripherally with a temporal convexity, leaving behind a central zone of transient blindness: a so-called scintillating scotoma (■ Fig. 16.1). Other symptoms of aura include slowly ascending, from distal to proximal, disturbances of sensation in the extremities, dysarthria (disturbances of articulation), or aphasia (disturbances of language expression or recognition), hemiparesis, and complex neuropsychological deficits, especially in the visual system. These include, for example, changes in color perception, changes in the perceived sizes of objects, loss of movement perception, and visual hallucinations (see Chap. 13). Aura symptoms develop slowly over a period of 5 to 10 min, and as a rule, last at most for an hour before subsiding. In some cases, aura symptoms occur without a subsequent headache.

Unusual Types of Migraine

There are several unusual types of migraine. In basilar artery migraine, the auras reflect disturbances in the blood supply to the brainstem and cerebellum. Symptoms include diplopia, vertigo, tinnitus, paresthesias in the face, ataxia, and quadriparesis.

Ophthalmoplegic migraine takes the form of an oculomotor disturbance with ptosis and diplopia.

! Note

The diagnosis of ophthalmoplegic migraine requires the urgent exclusion of an aneurysm at the origin of the posterior communicating artery.

In purely retinal migraine, ischemia of the retina or the anterior optic nerve can produce monocular visual field defects of varying severity, up to periods of transient amaurosis. The differential diagnosis includes amaurosis fugax, caused by retinal emboli arising from an atheromatous plaque in the carotid artery or from a valve in the heart. There are a small number of documented reports in which the sequence of events in retinal migraine were recorded by fluorescein angiography, which demonstrated spasms of the retinal arterial tree lasting for several minutes, followed by a period of rebound vasodilation.

Treatment of Migraine

The treatment of migraine is guided by two strategies. In the first, a prophylactic drug is used for long-term suppression. For example, regular use of beta-blocker (especially metoprolol) can be tried, if any one of the following occurs:

- The attacks are described as lasting for longer than 48 h.
- The use of specific antimigraine medications provides only temporary relief.
- The intensity of the pain is unbearable.
- The attacks occur three or more times a month.
- The attacks are not otherwise manageable.

Acute management of individual attacks is usually successful for pain of a moderate intensity, using an initial dose of metoclopramide followed by a nonsteroidal anti-inflammatory drug (NSAID). The use of NSAIDs alone (i.e., without metoclopramide or a similar agent) is seldom adequate, since the analgesics are frequently not absorbed from the gastrointestinal tract because of poor or absent gastrointestinal motility. For more severe attacks, use of ergotamine preparations or of serotonin agonists (e.g., sumatriptan) can be effective. The triptans have a beneficial effect, reducing nausea and vomiting, photophobia, and phonophobia. Their disadvantage is a short half-life, and they are contraindicated in coronary ischemia, Raynaud's syndrome, and hypertension.

Cluster Headache

Definition

Cluster headache (also called **erythroprosopalgia**) is characterized by its occurrence within specific, time-limited periods that last from 2 weeks to 2 months (clusters), separated by longer, asymptomatic intervals. The individual attacks are always unilateral and last from 30 to 90 min. They occur frequently with an almost clock-like periodicity and for a few patients always at the same time, usually during sleep. The intensity of the pain is severe and often unbearable. The quality of the pain is described variously as "boring" or "piercing," and is concentrated in the retro-orbital and periorbital regions. There are typical autonomic paraphenomena, including rhinorrhea, ptosis, miosis, lacrimation, and facial flushing. Patients with cluster headache do not withdraw, as is common among migraineurs. They pace restlessly back and forth, finding no rest until the attack subsides.

In the course of time, a chronic form of cluster headache can develop, in which the individual cluster periods lose their time-limited character, becoming more or less continuous. Triggering factors include alcohol, nitroglycerin preparations, high altitudes, or intense sunlight. With a prevalence of 0.04 to 0.09%, cluster headache is an uncommon disorder, and it affects men much more frequently than it does women (8:1).

In the differential diagnosis, cluster headache is most frequently confused with trigeminal neuralgia, though as a rule the unilateral pain of tic douloureux is more commonly referred to the jaw or the ear. The stabbing pains of trigeminal neuralgia last only a fraction of a second to a few seconds.

At the first onset of cluster headaches, the attacks can be confused with acute angle-closure glaucoma, given the retrobulbar or retro-orbital distribution of pain. During the diagnostic workup, a firmly palpable resistance to palpation of the globe supports diagnosis of an acute glaucoma. In addition, a dissection of the carotid artery can present with severe unilateral pain, ptosis, miosis, and a largely retrobulbar distribution of pain. Fortunately, it is also usually accompanied by other signs and symptoms of neural dysfunction that allow a clear distinction to be made.

Cluster headache is one of a group of primary headache disorders termed the trigeminal autonomic cephalalgias (TACs) which are characterized by strictly unilateral pain in the somatic distribution of the trigeminal nerve and ipsilateral autonomic signs, which reflect activation of the parasympathetic pathway (Horner's syndrome with miosis and ptosis, conjunctival injection, with nasal congestion, rhinorrhea, and swelling of the eyelid, but with normal sweating in the face). Further candidates are paroxysmal hemicrania (5–15 attacks per day, lasting 2–30 min), SUNCT – *s*hort-lasting *u*nilateral *n*euralgiform headache with *c*onjunctival ingestion and *t*earing – (2–200 attacks/hour, lasting 5–250 s), and probably the hemicrania continua with continuous headache and a very good response to indomethacin.

Treatment of Cluster Headache

Acute attacks of cluster headache can be effectively aborted by inhalation of 100% oxygen (7 l/min for 15 min). Alternatively, topical intranasal application of lidocaine or subcutaneously injected sumatriptan can be effective.

The management of individual attacks, however, is a temporary solution at best, and a means for aborting the cluster is needed. This can often be done with prednisone, using 60 to 80 mg/day. For prophylaxis, the calcium channel blocker verapamil can be started at a low dose, with gradually increasing doses to a maximum of 240 mg/day. Psychotherapy and physical therapy have no recognizable benefit.

Raeder's Paratrigeminal Syndrome

Definition

Paratrigeminal syndrome has many different causes. It is recognized as an association between a lesion affecting the first division of the trigeminal ganglion and a deficit in the sympathetic innervation of the ipsilateral eye. In addition to sensory loss and pain in the areas served by V_1, there is also Horner's syndrome, with miosis and ptosis but with normal sweating in the face. The original series reported by Raeder included cases of aggressively invasive neoplasms in the middle cranial fossa.

Tension Headache

Definition

By **tension headache**, we mean a holocephalic headache of a dull, oppressive character having a low to intermediate intensity, with low-grade light and sound sensitivity, occasionally producing nausea, but not vomiting. The head pain appears to be driven by increases in muscular activity that are associated with various forms of emotional tension. Aura symptoms, such as visual impairment or paresthesias, are not found. The pain is described as a "tight band encircling [the] head." By definition, an episodic tension headache, occurring less than 15 days a month, is distinguished from a more frequent or daily, chronic form.

Tension headache is, after migraine, the second most common form of primary headache, meaning that its symptoms are not thought to be caused by some underlying disease. It can present as episodic or as chronic. About 40 of all people are affected. The disorder usually begins at between 25 and 30 years of age. Women are more commonly affected than men are.

Unlike migraine, the pathophysiology of tension headache is poorly understood. It is often paired with terms such as vasomotor headache, muscle-contraction headache, etc.. Controlled studies have been reported showing that the tonus of pericranial muscles is elevated during tension headaches, but it is not correlated with the intensity of the pain. It is thought that a change in the sensory threshold level of a central nociceptive system is responsible for this type of headache.

In the differential diagnosis, a number of disorders should be considered. These can lead to similar types of headache and include frontal sinusitis, obstructive hydrocephalus, slowly growing brain tumors, subdural hematomas, and pseudotumor cerebri. In addition, headaches similar to those of the tension headache can be caused by chronic use of analgesics, ergotamine, arterial hypertension, a number of metabolic/endocrine disorders, infections, and substances that can directly elicit the sensation of pain, such as alcohol, nitrates, calcium channel blockers, and organic solvents.

Management of Tension Headaches

Episodic forms of tension headache are usually relieved by the readily available over-the-counter NSAIDs including aspirin, ibuprofen, naproxen, and acetaminophen. For chronic forms of tension headache, relief can often be found with daily use of tricyclic antidepressants, such as nortriptyline or amitriptyline. Effective doses are usually one third or less of those used in the treatment of depression. Starting with low doses (10 mg) taken at bedtime and then gradually increased, relief is usually experienced within a few weeks. Maximal doses for the management of headache should not exceed 100 mg daily. There can be a troublesome side effect of weight gain, when using amitriptyline, but nortriptyline is not thought to have this effect.

Venous Sinus Thrombosis

Thrombosis of the cerebral venous sinuses can be a diagnostic challenge for neurologists and ophthalmologists alike. It often presents as subacute, spontaneous head pain that awakens the sufferer from sleep and which gradually intensifies with a crescendo-like behavior. Thrombotic occlusion of the large cerebral venous sinuses is associated with substantial increases in cerebral spinal fluid (CSF) pressure, leading to frank papilledema. Additionally, neurologic deficits such as paraparesis of the legs or focal epileptic attacks can occur. Sometimes the initiating event is a bacterial sepsis, causing fever to be one of the signs at presentation. The pain is mostly holocephalic and diffuse, with a varying intensity, and it usually does not respond to over-the-counter analgesics. Characteristically, the pain increases when in a recumbent position, causing the pain to worsen during sleep, so that the patient awakens with pain. When the sufferer rises and maintains an erect position, the pain gradually subsides. MRI angiography is especially effective at detecting the cessation of blood flow in a venous sinus.

The cause of venous sinus thrombosis is often obscure and cannot be identified in about 25% of cases. Known risk factors include pregnancy and the puerperium, the use of oral contraceptives, and tobacco use.

Treatment of Venous Sinus Thrombosis

Treatment usually requires full anticoagulation with heparin, despite the risk of intracerebral hemorrhage. But with timely diagnosis and intervention, the prognosis is usually good. Treatment should be started in an inpatient setting, but once favorable levels of anticoagulation are obtained, most cases can be safely monitored as outpatients.

Pseudotumor Cerebri (Idiopathic Intracranial Hypertension)

Definition

Pseudotumor cerebri – more correctly, **idiopathic intracranial hypertension** – is a syndrome characterized by headaches, elevated intracranial pressure, papilledema, and normal CSF values with a normal CT and/or MRI scan showing no space occupying mass and especially no sign of venous sinus thrombosis (see Chap. 8).

The headaches of pseudotumor cerebri are typically holocephalic pressure sensations that are most prominent in the morning. The elevated CSF pressure, whose cause is yet to be determined, results in transient obscurations of vision and binocular papilledema that is often very severe. If untreated, it usually has a chronic and unremitting course that leads to optic disc gliosis and atrophy, ending in severe, bilateral loss of vision. The end stage of the disease causes visual field defects that look identical to those of end-stage primary open-angle glaucoma. Acuity may remain good when all but the central few degrees of visual field have been lost. (For a discussion of management of the pseudotumor cerebri syndrome, see Chap. 8).

Treatment of Pseudotumor Cerebri

Isolated headaches without visual disturbances in patients with a Pickwickian (morbid obesity) body habitus can be managed conservatively. Those few patients who find it possible to lose significant portions of body weight can usually enjoy a complete remission of the headaches. Although lumbar puncture (LP) will provide temporary relief of the pain, it is not a useful strategy for long-term management. In some patients, the first LP is followed by a complete remission of the syndrome. For some, however, it is necessary to treat a chronic, recurrent elevation of pressure with a carbonic anhydrase inhibitor, such as acetazolamide or methazolamide. If drug treatment is unsuccessful, surgical placement of a lumboperitoneal shunt may be necessary to control the pain. (Surgical fenestration of the optic nerve sheath can often reduce or eliminate the papilledema and preserve vision, but usually has no effect on the headaches).

Drug-Induced Chronic Headache

Definition

Drug-induced chronic headache is the frequent or daily occurrence of headache, associated with the regular daily use of analgesic drugs.

Patients with what is initially a form of tension headaches can, through the regular daily use of analgesics, develop an unremitting headache that is worse in the morning and is not associated with autonomic symptoms. Chronic use of analgesics by patients with migraine can also lead to an increased frequency and/or severity of their migraine attacks, and these can change into a steady, chronic pain that persists between attacks and which is different in character from the usual pulsating migrainous headache.

Treatment of Drug-Induced Chronic Headache

Chronic drug-induced headache can be managed only by an absolute cessation of analgesic use. During the period of withdrawal, only the use of medications to suppress nausea and vomiting is permissible.

Conclusion

Headache is always a serious problem when it comes on abruptly and unexpectedly. Nevertheless, there usually is sufficient time to allow taking of a complete history, which often clarifies the source of the problem. Only in a minority of cases is a neuroimaging study necessary:

- Abrupt onset of severe, unbearable head pain unlike any prior experience (subarachnoid hemorrhage)
- Fever and a stiff neck coincident with the onset of pain (abscess, purulent sinusitis)
- Atypical headache with focal neurologic signs
- Focal neurological symptoms (other than migraine aura)
- Papilledema or known or suspected elevations in CSF pressure
- Headache accompanied by the onset of seizures
- Psychopathologic behavior in a patient with no prior history of psychiatric disease
- Abrupt changes in the character of pain in a patient with an established history of headache

Pearl

Prior to any other diagnostic testing, it should be understood that a complete neurological examination is required, even if not by a neurologist.

Further Reading

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Kiel Headache Clinic. http://www.schmerzklinik.de

Chapter 17

Drug-Induced and Toxic Disorders in Neuro-Ophthalmology

E. Zrenner and W. Hart

Signal processing in the retinal photoreceptors, as well as in the cells and synapses of the afferent visual pathways, is controlled by a group of neurotransmitters, proteins, enzymes, and their metabolites that arise in complex cascades of chemical reactions to produce all the necessary functions of normal visual perception. Neurotropic drugs, toxins and some foods can interfere with these processes and their underlying structural components, thereby disturbing visual perception. In addition, there are non-neural metabolic processes that are needed to maintain the integrity of the visual system. For example, pigment epithelial cells, glial cells, and vascular components of the afferent visual pathway are all susceptible to the effects of drugs, toxins, and some foods. This mechanism is often responsible for subjective alterations in visual perception that are either expressed symptomatically by the patient or detected by specific visual function tests. Since a very large number of substances can specifically damage vision, we can discuss only the general principles of the diagnosis and management of toxic visual disorders. For individual cases of known or suspected toxic damage to vision, standard sources of reference should be consulted (see "Further Reading" at the end of the chapter).

This chapter describes the cell-specific disturbances of visual function, providing a rational basis for understanding toxic visual disorders, and outlines the typical symptoms of drug side effects that affect vision. This is meant to give the clinician a rational basis for diagnostic testing in cases of suspected toxic damage to the visual system.

Cell-Specific Alterations of Visual Function

Retinal Pigment Epithelium

The retinal pigment epithelium (RPE) has four principal functions: (1) phagocytosis, (2) vitamin A transport and storage, (3) control of retinal potassium content, and (4) protection from the effects of phototoxicity. So, RPE function can be damaged by inhibitors of phagocytosis, by drug dependent changes in cellular metabolism, by vitamin A deficiency or excess, and by substances that bind to melanin.

The melanin granules of the RPE bind tightly to certain substances, such as phenothiazines, glycosides, and antimalarial drugs such as chloroquine phosphate. This group also includes primaquine, pyrimethamine (Daraprim) and hydroxychloroquine (Plaquenil). Chloroquine phosphate binds strongly to the RPE with a half-life of 5 years, 80 times more strongly than it binds to the liver. This drug is not used for malarial prophylaxis alone, but it also plays an important role in the treatment of rheumatoid diseases (up to 4 mg/kg, or for hydroxychloroquine 6 mg/kg of body weight per day). At these maximal rates, a critical cumulative dose may be reached within 6 months.

Signs of chloroquine phosphate retinopathy (typically following a cumulative dose of 100 to 300 g) are:

- A relative paracentral scotoma, usually an annular perifoveal ring-shaped depression
- Loss of blue/yellow color discrimination
- RPE depigmentation in a target pattern matching the ring-shaped visual field depression (most easily seen during fluorescein angiography as window defects)
- Reduced electrooculography (EOG) potentials
- Reduced b-wave amplitudes and prolonged latencies of ERG responses (limited to relatively advanced cases)
- Depigmentation of the RPE in a ring-shaped pattern surrounding the fovea
- A bull's eye or target-shaped maculopathy becomes visible without special testing, but only in the later stages of irreversible visual loss

Particularly susceptible are those patients with low body weight and/or poor renal function. Care should be taken to avoid overdosing.

Chemotherapeutic agents that disrupt protein metabolism have an effect similar to the retinal toxicity of the antimalarial drugs. These include vincristine, vinblastine, alkylating agents, and some neurotoxic antibiotics, such as streptomycin and its associated derivatives.

Photoreceptors

Numerous substances can alter the phototransduction process by affecting individual steps of its enzymatically driven cascade. Common agents include the cardiac glycosides and chloramphenicol. The following are a few examples.

Inhibitors of Phosphodiesterase

Sildenafil (Viagra) acts as an inhibitor of phosphodiesterase (PDE) and can influence phototransduction when used at higher therapeutic doses. The effect is transient and quickly reversible. Other drugs with similar effects on PDE include theophylline and related agents used in the management of cardiopulmonary diseases.

Pearl

Potential visual effects of PDE inhibitors include dazzling photophobia, a blue discoloration of contrasting borders, dyschromatopsia (loss of hue discrimination), and phosphenes.

The differing spectral absorption properties of the retinal cones (short, long, and intermediate wavelength light sensitivity) are the basis for a variety of color vision disturbances: erythropsia, chloropsia, and tritanopsia.

Note

Chromatic sensations (Chromatopsia) and changes in color perception are among the earliest signs of drug-induced visual disorders.

Calcium Antagonists and Cardiac Glycosides

Calcium channel blockers and cardiac glycosides can affect control of intracellular calcium content, changing the light adaptation properties of retinal photoreceptors. The changes, however, are transient and reversible, and (in contradistinction to chloroquine) these drugs affect function in a relatively benign manner. Occasionally they produce symptoms of phosphenes, but in most cases, patients are unaware of the changes in their color vision. Detection of these hue discrimination deficits requires specific visual function tests of color perception, such as the desaturated Farnsworth D-15 (relatively cheap, quick, and easy), the Farnsworth-Munsell 100 hue, or the Nagel anomaloscope (relatively expensive, slow, and difficult). A number of testing devices are available that are intended to reduce the time needed to evaluate hue discrimination, but there has been only limited study of their clinical effectiveness.

Phenothiazine

Phenothiazine and related drugs have been widely adopted in the clinical management of the various psychoses. This group includes chlorpromazine, trifluoperazine (Stelazine), and promethazine. These drugs, when used chronically and in therapeutic doses, cause night blindness and retinal pigment dispersion, a consequence of damage to rod outer segments.

Bipolar Cells, Horizontal Cells, and Amacrine Cells

The outer and inner layers of the retina have numerous neurotransmitters and modulating substances (e.g., gamma-aminobutyric acid [GABA], glycine, acetylcholine, dopamine, serotonin, substance P, vasoactive intestinal peptide [VIP], somatostatin, nitric oxide [NO], and angiotensin-converting enzyme [ACE]). Altering the metabolism, release, or uptake of these substances can affect visual function. The following section discusses several common examples.

Alteration of GABA Metabolism by Antiseizure Medications

Some drugs used in the treatment of epilepsy can alter the metabolism of GABA, leading to disturbances of visual function. These drugs, including carbamazepine (Tegretol), phenytoin (Dilantin), and vigabatrin (Sabril), are known to disturb color vision, as measured by hue discrimination tests like the Farnsworth D-15. Vigabatrin can produce irreversible, concentric, peripheral visual field loss. Drugs that alter GABA metabolism are also likely at fault for changes in contrast perception by influencing the function of retinal horizontal cells. Chronic use of such agents can also lead to irreversible loss of these visual functions. It is advisable that patients on high doses or long-term use of these drugs be seen regularly for ophthalmic visual testing.

Alteration of Dopamine Metabolism by Drugs and Heavy Metals

Many drugs that are known to affect the metabolism of dopamine can produce changes in retinal function. Antipsychotic drugs, such as phenothiazine, haloperidol, and dopamine D2 antagonists are known to produce changes in retinal function. Similarly, heavy metal intoxication, by lead for instance, hinders the activity of dopamine synthesis. Since dopamine is of central importance in the function of rod-specific amacrine cells (A II amacrine cells) heavy metal poisoning results in changes to rod dominated neural signaling in the retina, as reflected in the detectable alterations to scotopic ERG potentials or in contrast sensitivity. Histologic preparations of the retinas of nonhuman primates that have been given toxic doses of lead have shown significant morphological changes in rod photoreceptors and their afferent retinal pathways.

Retinal Ganglion Cells

Retinal ganglion cells serve a diversity of neural tasks: the parvocellular system of cone dominated (and small) ganglion cells mediates the perception of color and the higher levels of spatial acuity, while the magnocellular ganglion cells respond to changes in visual stimuli involving image motion and contrast. Drugs that affect glial cell function, e.g., ethambutol, can lead to a variety of changes in the parvo- and magnocellular systems.

Pearl

Ganglion cell damage by ethambutol/myambutol leads to:

- Acquired dyschromatopsias (best found with the desaturated Farnsworth D-15 test), which are an early symptom
- Changes in color matching by anomaloscopic measures (not ordinarily available in most clinical settings)
- Loss of contrast perception
- Visual field loss (constriction and/or central and cecocentral scotomas)
- Loss of acuity

Several months after cessation of ethambutol use, normal visual function often returns if optic atrophy has not already developed. Other agents that can lead to ganglion cell disease include chloramphenicol, methanol, quinine, thallium, and ergotamine derivatives.

Retinal Glial Cells

The retina has several types of glial cells: Müller cells, oligodendrocytes, and astrocytes. Müller cells are important for glutamate metabolism (in the uptake of the transmitter released by photoreceptors), as well as for the storage of calcium ions. Damage to glial cells, e.g., by the ammonia toxicity of the alcohol syndrome (caused by severe hepatic damage), produces marked changes in the electroretinogram (ERG). This arises as the result of damage to Müller cells, since the b-wave of the ERG is strongly determined by the function of the retina's Müller cells. A common symptom of altered color perception in this setting is an acquired tritanopia: loss of discrimination between hues that differ in their blue/yellow content.

Optic Nerve

Varieties of drugs have specific effects on the function of axonal transport. Lead poisoning, for example, leads quickly to the appearance of disc edema, concentric loss of visual field, and a loss of blue perception. In higher doses, ethambutol produces a toxic demyelination of ganglion cell axons, leading to a loss of optic nerve function, as detected by a loss of amplitude in visually evoked potentials, the development of central and cecocentral scotomas, and acquired dyschromatopsias. Similarly, damage to optic nerve function is produced by the toxic effects of isoniazid (INH), streptomycin, and chloramphenicol.

Central Nervous System

As has been outlined for retinal disorders, toxic and pharmacologic disturbances of visual function can also crop up in the central nervous system. In addition to neurotropic effects, many drugs can cause elevations in intracranial pressure, resulting in papilledema, such as following the administration of ergotamine (see below).

From Signs and Symptoms to Diagnosis

General Medical History

A detailed medical history is critically important for cases in which toxic or pharmacologic effects on vision are suspected. Malabsorption syndromes, accompanied by changes in color perception, can be early indications of metabolic diseases and lead to further investigation of possible endocrinologic or toxicologic disorders. It is particularly important to discover any history of prior disease. If hepatic or renal function are known to have been compromised, it is possible that some drugs will not have been metabolized or completely excreted, leading to toxic blood levels. In such cases, a parallel evaluation by the patient's primary care physician or internist is important. Following gastric resection or bypass procedures, the risk of a vitamin-deficiency syndrome increases, and may be the cause of a metabolic optic atrophy, e.g., by chronic vitamin B_{12} deficiency.

Determining the duration of prior periods of illness will help to rule out chronic overdosing of medications as a mechanism for visual loss. It is important to determine the doses and durations of use for particular medications, including antitubercular agents, such as ethambutol, and antimigrainous agents, such as the ergot alkaloids, which often produce disturbances of red/green hue discrimination. Chronic use of antimalarials in the treatment of rheumatologic diseases can result in damage to retinal mechanisms for blue/yellow hue discrimination. A history of drug use should include specific questions about the taking of analgesics, antibiotics, neuroleptics, cardiac glycosides, antiarrhythmics and antihypertensives, as well as sleeping medications (■ Table 17.1). Acquired color vision disturbances associated with these drugs are summarized in ■ Table 17.3.

Pearl

Tobacco use of only 30 g weekly can produce a form of cyanide intoxication, especially when hepatic detoxification of trace cyanide is weakened by chronic liver disease (alcoholism and heavy tobacco use are familiar companions).

Table 17.1. Presentation, etiologic considerations, and diagnostic strategies to use when drugs, alcohol, occupational, and/or recreational exposures are a suspected source of toxic damage to vision

Presentation	Etiologic considerations	Diagnostic strategies
Medications: Analgesics, antibiotics, psychotropic drugs, cardiovascular drugs, sleeping agents	Phagocytosis inhibitors, transmitter metabolism, faulty phototransduction, disturbance of pupillary function	
Tobacco/alcohol	Optic neuropathy, cyanide poisoning (trace)	B_{12} blood levels, B_{12} absorption, Schilling test
Occupational exposure		
Heavy metals, solvents, chemicals in workplace, excessive light exposure	Intoxication, retinal edema, inhibition of mitochondrial oxidase enzymes, disturbances of accommodation	Toxicologic tests, bone marrow smears (especially when lead poisoning is suspected), fluorescein angiography
Pastime activities		
Exposure to solvents in poorly ventilated rooms, gardening (pesticides)	Intoxication	

Vitamin B_{12} deficiency, as in megaloblastic anemia, can lead quickly to a metabolic optic neuropathy. Careful static perimetry of the central visual field is particularly helpful at uncovering the characteristic shape, size, and location of scotomas that are sharply defined, often lancet-shaped and deep, extending linearly from the nasal border of the physiologic blind spot to the point of fixation (see Chap. 4). Often the risk of toxic disease is discovered when taking a history of occupational exposures. Chronic exposure to heavy metals like lead and silver that are common in metal working industries or in commercial printing plants, can lead to a toxic optic neuropathy that becomes apparent, sometimes years after leaving the trade. Skeletal accumulation of lead can sometimes be found through careful radiologic study. Blood levels of lead that are often only marginally elevated can cause an optic neuropathy following years of chronic exposure. Inhalation of solvent vapors like benzene or methyl alcohol can lead to occupationally acquired dyschromatopsias. Another occupational hazard to be considered is that of retinal phototoxicity, as for operators of instruments with very powerful light sources (e.g., laboratory engineering instruments, lasers, or photo projectors).

Some Peculiarities of the Ophthalmic History

Additional consideration should be given to some specifically ophthalmic problems, as outlined in ■ Table 17.2. Assessment of the duration and course of illness can help to differentiate between congenital and acquired forms of visual loss. Acute processes are more likely to be acquired disorders, while a history of stable deficits in vision is more consistent with a heredofamilial disorder. Retinal degenerations most often have a gradually increasing course of visual loss; toxic disorders present as bilaterally symmetric diseases; and nontoxic, acquired diseases (vascular, inflammatory, or neoplastic) are more often asymmetric. Loss of vision with clear refractive media in company with an acquired dyschromatopsia suggests a toxic disorder.

Note

Other symptoms frequently associated with toxic amaurosis include paresthesias, headache, vertigo and loss of hearing.

Important Details of the Ophthalmic Examination

When neuro-ophthalmic problems are recognized or suspected, the basic ophthalmic examination should give as much weight to evaluating eye movements, pupillary function, and accommodation, as it usually does to deposits on lens, iris, and corneal surfaces. Ophthalmoscopy may find the toxic effects of drugs (e.g., narcotics containing methoxyflurane or methadone) that are metabolized into oxalates, resulting in deposits with an albipunctate appearance, often described as a "talc retinopathy." Macular edema and toxic optic neuropathies with associated optic disc pallor can be produced by some medications, such as during the course of therapy with antibiotics like chloramphenicol, and tetracycline.

Table 17.2. Typical ophthalmic presentation in cases of intoxication or drug side effects, etiologic considerations, and diagnostic strategies

Ophthalmic presentation	Etiologic considerations	Diagnostic considerations and strategies
Duration/course	Acute: more likely acquired Chronic and stable: more likely heredofamilial	
Tobacco/alcohol abuse	Occupational intoxication less likely	
Strict symmetry	Intoxication more likely	
Hemeralopia with clear ocular media	Intoxication or heredofamilial retinopathy	Electrophysiology and/or dark adaptometry
Nyctalopia	Tapetoretinal degenerations or intoxication possible	Electrophysiology and/or dark adaptometry
Dyschromatopsias	Vascular, toxic, demyelinating, and compressive optic neuropathies, and/or retinopathies	Internal medical and/or neurological consultation

Pearl

Optic disc edema and elevated intracranial pressure are known to be produced in some patients by the systemic administration of corticosteroids, nalidixic acid, tetracycline, and toxic doses of vitamin A. Exposure to hexachlorophene, dinitrobenzene, dinitrochlorobenzene, disulfiram, INH, thallium, and vincristine can cause a combined optic neuropathy and peripheral neuropathy.

Clinical Workup of Suspected Toxic Disorders

The most important signs and symptoms that are likely to be present when dealing with a toxic disorder include loss of Snellen acuity, color vision impairment, changes in the ERG/EOG/visually evoked potentials (VEP), visual field constriction (organic, not functional), photophobia, and poor dark adaptation.

Loss of Acuity and Central Scotoma

There are a number of substances that preferentially damage the papillomacular bundle and its retrobulbar axons, causing central scotomas and loss of Snellen acuity.

Pearl

The most important of these include barbiturates, benzene, lead, tobacco-alcohol syndrome, ethambutol, and methanol.

Loss of Peripheral Visual Field

Agents that typically damage the peripheral visual field, without necessarily affecting acuity, include lead nalidixic acid, phenothiazine, vigabatrin, chloramphenicol, nitrofurantoin, quinine, and the salicylates. Ring and arcuate scotomas are typically associated with chloroquine, INH, and streptomycin.

Change in Color Vision

An acquired dyschromatopsia is frequently the presenting finding of toxic damage to the retina and/or optic nerve. The principal drugs and chemical agents associated with damage to color vision are summarized in ■ Table 17.3. The toxic dyschromatopsias are associated with damage to the function of the three types of cone photoreceptors (short-wavelength-sensitive blue cones, medium-wavelength-sensitive green cones, long-wavelength-sensitive red cones) or to their downstream neurons. The toxic effect on color vision is determined in part by the variable densities of cones, and by variable susceptibility of the downstream ganglion cell axons to toxic damage.

For example, blue cones have a particular spatial distribution in the retina unlike any other cone system: There are no blue cones in the fovea, and their density is greatest at about 2.5° of retinal eccentricity. Toxic retinopathy commonly presents as a loss of perifoveal visual field (ring-shaped scotoma), which in turn produces greater impairment of blue/yellow than of red/green hue discrimination. A drug that commonly causes this pattern of damage is chloroquine. The patient will notice problems with reading that are far greater than one would expect, based on their retained foveal function and good Snellen acuity. The paracentral loss of vision disrupts the fluency of reading, since only letters and syllables can be seen, rather than whole words or phrases (see Chap. 24 for a more complete explanation). Hue discrimination tests (such as the desaturated Farnsworth D-15) will find a greater impairment of blue/yellow discrimination with preservation of red/green discrimination.

Drugs like ethambutol, however, damage the pathways fed by foveal cones, resulting in an early loss of Snellen acuity and relative or absolute central scotomas. Since the foveal cone matrix of red- and green-sensitive cones is devoid of blue cones, damage to the fovea or its afferent projections (with at least some preservation of the extrafoveal portions of the central visual field) results in a dyschromatopsia marked by loss of red/green hue discrimination and with relative preservation of blue/yellow hue discrimination. Again, the Farnsworth D-15 test is not prohibitively time-consuming, and it will detect a preferential loss of red/green hue discrimination. These patterns of changes in color vision are characteristic of the early stages of retinal or neural toxicity, at a time when their detection is most valuable. Progression of the damage, causing a scotoma that erases the central 5 to 10° of visual field, results in an anarchic loss of color perception with no useful hue discrimination at all. Typically, if acuity has already been reduced to 20/200 or worse, hue discrimination tests will be of no value. Thus, color vision testing of this sort is best for evaluating patients in the early stages of their diseases, but may become useless as the visual damage progresses. The use of color vision testing in congenital and acquired dyschromatopsias is discussed more completely in Chap. 6.

Reduced Contrast Sensitivity and/or Photophobia

Agents that depress neural function in a general way often produce a loss of contrast sensitivity. When the effect is most pronounced in the central visual field, patients will often complain of severe photophobia. This is due to loss of the cone-dominated portions of the visual field with preservation of the rod-dominant portions. In this case, sufferers can see comfortably at low levels of illumination, but they are effectively blinded at higher levels of brightness (hemeralopia).

Table 17.3. Common drug-induced disturbances of color vision. (Expanded from data reported by Pokorny et al. 1979)

Medication	Type I Acquired protan red/green dyschromatopsia	Type II Acquired deutan red/green dyschromatopsia	Type III Acquired tritan blue/yellow dyschromatopsia
Antidiabetics (oral)		+	
Antipyretics		+	
Phenylbutazone		+	
Nitrofurantoin and its derivatives	+	+	
Nalidixic acid		–	
Phenothiazine	+?		+
Quinoline and its derivatives	+	+	+
Quinine	+	+	
Sulfonamides		+	
Tuberculostatics		+	
Dihydrostreptomycin		+	
Ethambutol		+	
Isoniazid		+	
PAS		+	
Streptomycin		+	
Arsenic		+	
Chloramphenicol		+	
Cyanide		+	
Digitalis	++	+	+
Disulfiram		+	
Ergotamine		+	
Erythromycin			+
Ethanol		+	
Indomethacin			+
Lead		+	
MAO inhibitors		+	
Indomethacin		+	
Sildenafil			+
Thallium		+	
Trimethadon			+
Vincristin		+	

PAS Para-aminosalicylic acid, *MAO* monoamine oxidase

Abnormal ERG

Disturbances of the phototransduction processes and/or of the synaptic processing in the retinal neuronal network are easily detectable by ERG testing. Changes in the ERG often allow a distinction between rod- and cone-dominated damage caused by toxic exposures. Reduced amplitude and prolonged latency of ERG responses are typical signs of retinal toxicity and can be used to evaluate known or suspected toxic damage. Agents that often affect the ERG include phosphodiesterase inhibitors like sildenafil, phenothiazine and some tricyclic agents (thioxanthene derivatives), haloperidol, diazepam, imipramine, trimethadione, and others.

Abnormal EOG

The EOG provides specific information about the function of the pigment epithelium/photoreceptor complex, and is especially useful for detecting pigment epithelium damage of the kind produced by the antimalarial drugs, such as chloroquine (Aralen) and hydroxychloroquine (Plaquenil).

Abnormal VEP

Toxins that damage the myelin sheaths of ganglion cell axons (e.g., ethambutol, lead), especially those that have their greatest effect on the papillomacular bundle, produce changes in visually evoked cortical potentials. Looking for these changes with the VEP test is particularly valuable when monitoring long-term use of drugs like ethambutol.

Abnormal Dark Adaptation

Drugs like vincristine or those of the phenothiazine group commonly cause a depression of light sensitivity and a change in the shape of the dark adaptation curve. These agents cause damage to the pigment epithelium/photoreceptor complex, alter the kinetics of the rhodopsin cycle, and change the synaptic behavior of horizontal cells, aggravating the problems with dark adaptation. When such a drug side effect is suspected, a very careful drug history and ophthalmic examination should give a clue as to the agent, the site, and the mechanism of toxic damage to vision.

Abnormal Pupils

Directly acting adrenergic agents, such as adrenalin and phenylephrine, as well as indirect adrenergic agents, such as tyramine and cocaine, stimulate pupillary dilation, while cholinergic agents, such as pilocarpine and physostigmine, stimulate pupillary constriction.

Anticholinergic agents block neural transmission at parasympathetic terminals, leading to pupillary dilation. This group includes a number of antispasmodic agents used to reduce gastrointestinal motility, as well as the belladonna alkaloids, that pose a threat of acute angle closure glaucoma in eyes with narrow chamber angles. Mydriasis can occur following the use of antiparkinsonian medications, some antihistamines, tranquilizers, antipsychotic and antidepressant medications, and miosis can be produced by cholinesterase inhibitors (used in the management of myasthenia), antihypertensive agents, and opium derivatives. Presenting symptoms caused by changes in refraction and/or accommodation are known to occur in response to the use of a number of medications. Thus, the use of an anticholinergic or adrenergic agent can lead to a loss of dioptric power in the lens and a reduction in the amplitude of accommodation in addition to producing a pupillary mydriasis. Parasympathomimetic and sympatholytic agents by contrast can lead to a spasm of accommodation with increasing dioptric power of the lens and an associated miosis. Systemically administered agents must be given at unusually high doses to cause these problems in most people, but some patients have a heightened susceptibility by virtue of anatomically narrow anterior chamber angles, for instance.

Pearl

Acutely transient myopia without miosis or spasm of accommodation can also occur in patients taking salicylates, codeine, sulfonamides, tetracyclines, some diuretics, carbonic anhydrase inhibitors, and some antipsychotic medications.

Abnormal Lid and/or Eye Movements

Ptosis has been reported as a side effect after the use of barbiturates and other hypnotic or sedative agents, such as chloral hydrate, as well as by heavy metals, vinca alkaloids, muscle relaxants, and sympatholytic and ganglionic blocking agents.

Blepharospasm and involuntary blinking can be signs of chronic poisoning by cholinesterase inhibitors, such as the organophosphate insecticides like Malathion. A widening of the palpebral fissures with upper lid retraction may be a sign of drug-induced hypersympathotonia following ingestion of amphetamines. Hypermetric saccades can be brought out by overdoses of monoamine oxidase (MAO) inhibitors, while slowing of eye movements can be seen following intravenous administration of central nervous system depressants like the benzodiazepines.

Higher-order centers of eye movement control are affected by a very large number of drugs, but most commonly by sedatives and anticonvulsants. Even relatively low doses of these agents can cause substantial changes in eye movements, especially when the affected patient is already ill. Careful history taking of drug use and access to appropriate reference materials are sometimes necessary for correct diagnosis of an iatrogenic problem.

Conclusion

Binocular visual disturbances of uncertain origin (■ Table 17.4) can have many different causes, including the unintentional side effects of medications and/or exposure to environmental toxins. The retina and afferent visual pathways, by virtue of their many neuronal functions, often act as an early warning system of threatening exposures to toxins. The ophthalmologist has available a large number of instruments for the detection of these signs. Nevertheless, in specific instances of suspicion, a direct causation can be difficult to prove, requiring a detailed assembly of findings to build a circumstantial case. Occasionally, contact with a poison emergency call line (■ Table 17.5) or with a manufacturer of the suspected agent can be helpful. For suspected occupational exposures, contact with an industrial institute of labor medicine can often uncover previously unrecognized risks to health. When the suspicion of toxic exposure is persuasively strong, reports should be filed with the appropriate state and local governmental agencies. Most important for the managing ophthalmologist is to at least consider the possibility that there is a toxic cause of the visual problem, and to initiate the use of appropriate tests to better clarify the cause.

Table 17.4. Binocular visual disturbances of uncertain cause

Historical features to explore	Are objective signs found?
Drugs: • Which? Dose? How Long? **Toxic exposures:** • Occupational? Ingested? • Known diseases that affect absorption or metabolism of toxins? • Unusual diet?	**Frequent signs include:** • Loss of visual acuity? • Change in color appearances? • Visual field defects? • Poor dark adaptation? • Is the ERG, EOG, or VEP altered?
Are there characteristic ophthalmic symptoms? • Photophobia? • Altered color perception? • Visual field loss? • Blurred vision?	**Additional clues to examine:** • Change in pupillary function? • Loss of accommodation? • Motility disturbance?
Are there characteristic neurologic symptoms? • Paresthesias? • Syncope? • Headache? • Hearing loss?	**Classify by known associations:** • Consult toxicologic reference texts (Grant and Schumann 1993). • Call your local poison control center (use the following URL to find the nearest help: http://www.aapcc.org/findyour.htm). • Call the manufacturer of the suspected substance, if known. **For occupational exposures:** • Consult with occupational physician. • File reports with local departments of health.

ERG electroretinogram, *EOG* electrooculogram, *VEP* visually evoked potential

Table 17.5. Poison control centers

Given the numerous possibilities for agents in any case of intoxication, it is important to consult, in addition to the standard reference texts like W. Morton Grant's Toxicology of the Eye (W.M. Grant and J.S. Schuhman, Charles C Thomas Pub., Ltd., 4th edition, August 1993), databases of both ophthalmic and systemic drug- and toxin-induced disorders. The following internet resources can be of help:

- **http://www.cdc.gov/niosh/homepage.html**
  is a very good source of information about toxins as occupational hazards.
  The site is maintained by the National Institute for Occupational Safety and Health (NIOSH) and is a part of the Centers
  for Disease Control and Prevention (CDC)
- **http://www.eyedrugregistry.com**
  is the Web address of the National Registry for Drug-Induced Ocular Side Effects:
  National Registry of Drug-Induced Ocular Side Effects
  3375 SW Terwilliger Blvd. Portland, OR 97239-4197, USA
- **http://www.nei.nih.gov/**
  The National Eye Institute provides convenient and useful links to multiple sources of information
  about toxicology, as it relates to vision.
- **http://toxnet.nlm.nih.gov/**
  is a good starting point when searching for known toxins, this site links to a wide range of databases for toxicology, hazardous chemicals, and related subjects.
  The various databases can be searched in unison, providing a convenient
  and comprehensive source of information.
- **http://www.druginfozone.org/**
  – In the UK this web site [as described by M. Wake
  and L. Lisgarten at http://pfonline.com/students/tp2001/internet/html] is run by the London and South Eastern Drug Information Service. It provides up-to-date news, current awareness bulletins, and monthly updates on the latest published material for 44 major drug topics such as drug interactions, pain, and poisoning. The material for these topics is taken from the Pharm-line database, which indexes English language pharmaceutical and medical journals. It has a very good links page.

Further Reading

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Chapter 18

Hereditary Disorders of Neuro-Ophthalmic Relevance

D. Besch

Hereditary disorders of importance for neuro-ophthalmology include genetically inherited disorders of the posterior segment and afferent visual pathway that characteristically present as visual field defects, visual acuity loss, strabismus, or even complete blindness. These disorders have significant social and economic importance with lifelong consequences for the afflicted patient. The prevalence of inherited retinal disorders is approximately 20 cases per 100,000 people.

Decoding of the human genome has been the most important single advance in the study of inherited disorders. In the last 16 years, 132 genes of significance for the development of retinal degenerations and optic atrophy have been identified, and 53 of them have been mapped to their chromosomal locations (as of January 2007, according to the Retinal Information Network: http:/www.sph.uth.tmc.edu/Retnet/). Using the various techniques of molecular genetics, genetic defects could be located, to specific chromosomal regions (mapped loci), often without knowing precisely which gene is at fault. Additionally, specific functional regions of a DNA segment (= gene) could be identified to carry the changes (mutations) that encode for the traits of a particular disease (■ Fig. 18.1).

It is now recognized that mutations in various, separate genes can be expressed in phenotypes that appear to be identical disorders, as for example with retinitis pigmentosa. Alternately, it is known that a variety of differing mutations within a single gene can produce disorders that appear to be entirely different diseases. A few inherited ocular diseases have been traced well enough so that their specific biochemical changes in cellular metabolism are known, and the mechanism that produces their phenotypic expression is fully understood. The changes in cellular metabolism caused by the genetic defect then produce the various morphological and visibly recognizable signs of disease in the retina and/or the afferent visual pathway.

Specific diagnosis of hereditary ocular diseases require; very careful history taking, recognition of ophthalmic signs and typical visual function losses, collection of genetic information (family history of inherited disorders and identification of carriers), associated symptoms, and appropriate laboratory testing.

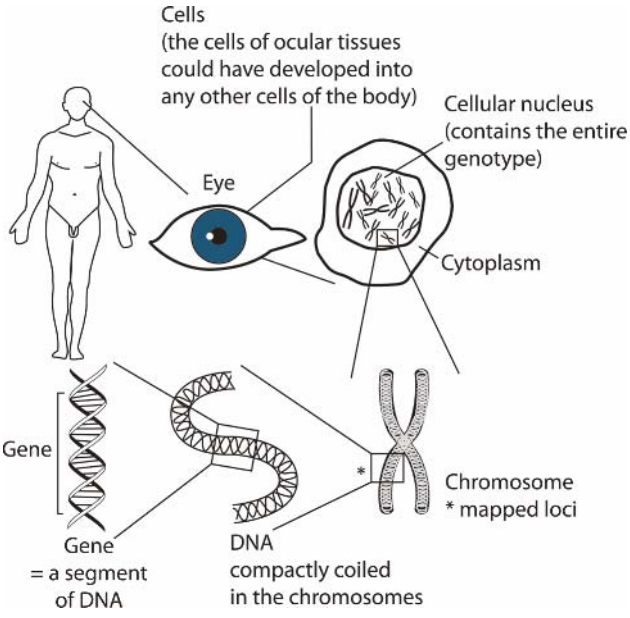


Fig. 18.1. Location of a gene. Diagram of chromosomes in a cell, of a particular chromosomal region mapped loci, and a functional DNA segment (identified gene). (Adapted from: C. Fesch: Genetische Tests. Fischer, Frankfurt 2000)

Therapeutic Options

Despite having a better understanding of genetic mutations and the disease patterns they cause, there have been to date no discoveries of treatments that can correct the damage to the underlying metabolic processes or reverse the course of their associated loss of visual function. There have been some plausible reports of partially effective treatment of

various forms of retinal dystrophies with the use of vitamin therapy. Thus, for specific types of retinitis pigmentosa the use of vitamin A palmitate is now recommended, and mitochondrially inherited abnormalities of respiratory enzymes, such as in Leber's hereditary optic neuropathy, may benefit from correction of low levels of vitamin B_{12}. In addition, exogenous risk factors that further burden an already-weak cytochrome oxidase chain should be avoided, such as foods containing trace levels of cyanide, abuse of alcohol, and exposure to nicotine.

Lens filters, for protection from higher levels of light and improvement of contrast sensitivity, are a rational option that can be of help in the management of some hereditary retinal diseases. Additionally, cataract extraction at an appropriate time and the use of magnifying reading lenses might improve visual acuity in some cases.

Experiments with various animal models of retinal disease and histologic study of human retinal tissues in recent years have brought to us a better understanding of the pathological changes that characterize inherited retinal degenerations. Eexperiments are underway to study the feasibility of the electronic retinal implants, transplantation of pigment epithelium or photoreceptor tissue/cells as well as of use of neuroprotective growth factors, and the potential use of somatic gene therapy.

Rare retinal dystrophies, such as Refsum's disease, gyrate atrophy, or abetalipoproteinemia (Bassen-Kornzweig syndrome) are metabolic disorders that can be partially countered with vitamins and dietary changes, which can even reverse some of the visual symptoms. For other inherited disorders, such as retinoblastomas, von Hippel Lindau syndrome, and Alport's syndrome some conventional therapies are known to be helpful, including surgery, irradiation, cryotherapy, and laser therapy.

Systemic disorders can present initially with ocular signs and/or symptoms, leading to an early diagnosis of such diseases as pseudoxanthoma elasticum and familiar polyposis. This sometimes provides the opportunity for early use of treatment strategies, such as colectomy for the avoidance of bowel carcinomas in patients with familiar polyposis.

Tabular Summary of Hereditary Disorders of the Posterior Segment and Afferent Visual Pathways

The table below that summarizes the features of hereditary ocular diseases of the retina and optic nerve has been restricted to the most important entities. For a more complete reference, the resources listed in ■ Table 18.1 provide a rich source of additional information held in on-line databases.

■ Table 18.2 briefly lists the typical symptoms for each disease and gives estimates of the frequency of each disorder and its mode of inheritance.

In addition, gene locations and genes that have already been identified are listed (as of 2003). As an example, chromosome 6p21.1 is the locus for the *RDS/peripherin* gene (■ Fig. 18.2): The gene was localized on chromosome 6, the short arm (p = short arm, q = long arm), in region 21.1 (arrow).

Table 18.1. Databases and Internet addresses with useful information about hereditary ophthalmic disorders

Online Mendelian Inheritance in Man (OMIM): http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM&cmd=Limits
Retinal Information Network (RetNet): http://www.sph.uth.tmc.edu/Retnet/
Retina International's Scientific Newsletter: http://www.retina-international.org/sci-news/index.htm
VMD2 Mutation Database: http://www-huge.uni-regensburg.de/VMD2_database/index.php?select_db=VMD2
A human mitochondrial genome database: http://www.mitomap.org/

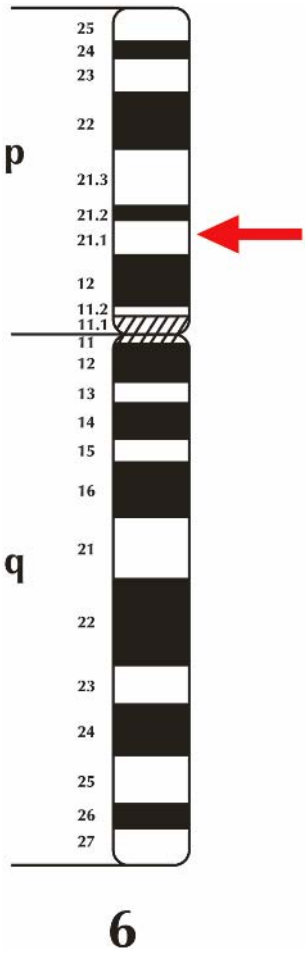


Fig. 18.2. The *RDS/peripherin* gene is know to be located on chromosome 6p21.1, on the short arm (*p*), of chromosome 6 in the region 21.1 (as indicated by the *arrow*)

Conclusion

The consulting ophthalmologist plays an important role in arriving at a correct diagnosis and in advising the patient on how to cope with the social, familial, and occupational problems that these hereditary disorders can cause. Identification of the specific mutation in affected patients and their relatives is important in the differential diagnosis, and allows the physician a more rational basis for counseling the affected individuals.

Table 18.2. Hereditary disorders of the posterior segment and visual pathway (a partial listing as of 2003). *AD* autosomal dominant, *AR* autosomal recessive, *XR* X-linked recessive, *XD* X-linked dominant, *MT* mitochondrial, *penetrance* probability that a trait will be expressed (proportion of gene carriers showing phenotypic expression), *expressivity* degree to which an inherited trait is expressed

1. Peripheral retinal dystrophies – vitreoretinal dystrophies

Disorders	Frequency	Mode of inheritance	Symptoms (ocular/general)	Gene location	Gene name	Molecular genetic testing
Retinitis pigmentosa (RP) (nonsyndromic)	1:3,000–5,000	AR (84%) AD (10%) XR (6%)	Early nyctalopia, concentric visual field constriction and/or ring depression, and late loss of acuity, usually with an acquired blue/yellow dyschromatopsia Mild (retinitis paucipigmentosa or retinitis pigmentosa sine pigmento) to severe (bone spicule) ophthalmoscopic signs of damage to the pigment epithelium Optic atrophy (waxy yellow appearance of the optic discs), arteriolar narrowing, later development of cataracts and/or macular edema Variable rate of progression: AD usually has a mild course and occasionally has a sectoral expression (phenotypic mosaicism); XR has a poor prognosis Diagnosis often suggested by deficits discovered during dark adaptation, scotopic electroretinogram (ERG), and/or perimetric testing	**AR:** 4p12–cen 5q31.234 4p16.3 10q23 3q21–24 13q34 15q26 2q37.1 1q31–32.1 6p21.3 1p21–p13 6p21.1 11q13 2q14.1 15q23 1p31 **RP22:** 16p12.1–p12.3 **RP25:** 6cen–q15 **RP26:** 2q31–33 **RP28:** 2p11–p16 **RP29:** 4q32–q34 **AD:** 3q21–24 19q13.3 6p21.1 11q13 8q11–13 14q11 **RP9:** 7p15.1–p13 **RP10:** 7q31.3 **RP11:** 19q13.4	 *CNGA1* *PDE6A* *PDE6B* *PGR* *RHO* *RHOK* *RLBP1* *SAG* *CRB1* *TULP1* *ABCA4* *RDS/Peripherin* *ROM1* *MERTK* *NR2E3* *RPE65* RHO (30%) CRX RDS ROM1 RP1/ORP1 NRL IMPDH1	http://www.genetests.org/ (An informational service for physicians that is funded by the National Institutes of Health)

Table 18.2. (*Continued*) **1. Peripheral retinal dystrophies – vitreoretinal dystrophies**

Disorders	Frequency	Mode of inheritance	Symptoms (ocular/general)	Gene location	Gene name	Molecular genetic testing
				RP13: 17p13.3 **RP17:** 17q22–24 **RP18:** 1q13–21 **XR:** Xp11.3–22 Xp21.1 **RP6:** Xp21.3–21.2 **RP23:** Xp22 **RP24:** Xq26.9–q27	*PRPF31* *PRPF8* *RP2 (~20%)* *RPGR (10–20%)*	http://www.genetests.org/ (An informational service for physicians that is funded by the National Institutes of Health)
Leber's hereditary amaurosis		AR Occasionally AD	1. Congenital: infantile blindness, nystagmus, severe photophobia, and oculodigital manipulation behavior Fundus appearance: "salt and pepper" at first, later mimicking an RP appearance 2. Juvenile (also in juvenile RP): progressive loss of acuity during childhood The ERG is usually diagnostic.	**LCA1:** 19q13.3 17p13.1 **LCA2:** 1q31 **LCA3:** 14q24 **LCA4:** 17p13.1 **LCA5:** 6q11–q16 **LCA6:** 14q11	*CRX* *GUCY2D* *RPE65* *AIPL1* *RP*GRIP1	
Ocular albinism	1: 20,000–55,000	XR AR	Nystagmus, strabismus, poor acuity, hemeralopia. High myopia (20%), iris transillumination defects (absence of melanin in the posterior pigmented iris layer), and depigmentation of the retinal pigment epithelium Foveomacular hypoplasia or aplasia Central scotoma and other visual field defects Normal pigmentation of skin and hair Not progressive Carriers are occasionally microsymptomatic.	**OA1:** ***Xp22.32–22-2*** **OA2:** Xp11.4–p11.23 **OAR/OA3:** 6q13–q15	*OA1*	

Table 18.2. (*Continued*) **1. Peripheral retinal dystrophies – vitreoretinal dystrophies**

Disorders	Frequency	Mode of inheritance	Symptoms (ocular/general)	Gene location	Gene name	Molecular genetic testing
Congenital stationary night blindness (CSNB)		AR AD XR	Nyctalopia with an unremarkable fundus appearance, myopia, and sometimes strabismus Dark adaptation and ERG testing are usually diagnostic in complete CSNB [CSNB1]. Incomplete CSNB [CSNB2] marked by negative ERG (Schubert-Bornschein type), or no negative ERG (Riggs type)	**AR:** RDH1 12q13–q14 13q34 **AD:** 3p22 3q21–24 4p16.3 (CSNB3) **XR:** Xp11.4 (CSNB1) Xp11.23 (CSNB2) Xp21.1	 *RDH5* *RHOK* *GNAT1* *RHO* *PDE6B* *NYX* *CACNA1F* *RPGR*	http://www.genetests.org/ (An informational service for physicians that is funded by the National Institutes of Health)
Fundus flavimaculatus	About 50 cases have been described	AR Rarely AD	Multiple yellow flecks (lipofuscin deposits in the pigment epithelium) of the posterior pole. Juvenile macular dystrophy (Stargardt's disease) is found in about half of cases, and the remainder shows no apparent macular abnormalities.	6p12 1p22.2–21 6q13–15	*TUB* *ABCR* *IMPG1*	
Choroideremia		XR	Problems with poor night vision since childhood, progressive concentric loss of the peripheral visual field, followed by later loss of central visual function (by about age 40 years). Gradually spreading defects of the retinal pigment epithelium and choroid with initial sparing of macular function. Carriers often have mild deficits of the visual field, and/or an abnormal fundus appearance. The diagnosis is confirmed by the results of dark adaptation, scotopic ERG, and perimetric testing.	**CHM:** Xq21.3–22	*REP-1*	
Congenital (juvenile) retinoschisis	1:15,000–30,000	XR	Loss of visual acuity during childhood (0.3–0.1), small stellate cysts form convolutions in the macula, there is often elevation of the peripheral neuroretina (in half of cases and mostly in the inferotemporal quadrant), and vitreous veils, frequently accompanied by hyperopia, central scotomas, red/green dyschromatopsia. Signs include vitreoretinal hemorrhages, retinal detachments and cataracts. The ERG (loss of b-waves) is typical. There is little or no progression of the central visual changes.	**RS1:** Xp22.2	*XLRS1*	I

Table 18.2. (*Continued*) **2. Systemic and metabolic syndromes associated with retinitis pigmentosa**

Disorders	Frequency	Mode of inheritance	Symptoms (ocular/general)	Gene location	Gene name	Molecular genetic testing
Usher's syndrome	1:30,000	AR	Types I-IV: Type I: RP + deafness Type II: RP + inner ear deafness Type III: RP + progressive inner ear deafness Type IV: RP + inner ear deafness inherited in the XR mode	**USHIA:** 14q32 **USHIB:** 11q13.5 **USHIC:** 11p15 **USHID:** 10q21–q22 **USHIE:** 21q21 **USHIF:** 10q **USHIIA:** 1q41 **USHIIB:** 3p24.2–23 **USHIIC:** 5q14–q21 **USHIII:** 3q21–q25	 *MYOVIIA* *USH1C* *CDH23* *USH2A*	http://www.genetests.org/ (An informational service for physicians that is funded by the National Institutes of Health)
Bardet-Biedl syndrome, also called Laurence-Moon-Bardet-Biedl syndrome	1:15,000–160,000	AR Full penetrance with variable expression	Ocular: retinitis pigmentosa Nonocular: polydactyly, obesity, hypogenitalism and hypogonadism, mental retardation, frequent diabetes mellitus, hypertension, hypodontia, and renal hypoplasia	**BBS1** (50%): 11q13 **BBS2** (27%): 16q21 **BBS3:** 3p13–12 **BBS4:** 15q22.3–23 **BBS5:** 2q31 **BBS6:** 20p12	*BBS1* *BBS4* *MKKS*	
Kearns-Sayre syndrome (CPEO plus syndrome)		MT	Ocular: pigmentary retinopathy, ptosis and external ophthalmoplegia Nonocular: cardiac conduction defects, ataxia, pareses of facial, axillary and arm musculature, elevated protein content of the CSF, loss of hearing ERG, EEG, EKG, and muscle biopsy ("ragged, red fiber" appearance) are diagnostic	**KSS:** mtDNA deletion		

Table 18.2. (*Continued*) **3. Retinal dystrophies with predominantly macular or posterior pole abnormalities**

Disorders	Frequency	Mode of inheritance	Symptoms (ocular/general)	Gene location	Gene name	Molecular genetic testing
Vitelliform macular degeneration (M. Best)		AD with reduced penetrance and variable expressivity	Stage 1: vitelliform cyst in the macula (egg yolk appearance), normal acuity Stage 2: Breakdown of the cyst with pseudohypopyon formation and reduced visual acuity Stage 3: Cyst rupture, macular scarring with severe loss of macular function Electrooculography (EOG) testing and examination of younger members of the family help to confirm the diagnosis	**VMD1:** 8q24 **VMD2:** 11q13	 *Bestrophin/ VMD2*	http://www.genetests.org/ (An informational service for physicians that is funded by the National Institutes of Health)
Cone–Rod dystrophy (inverse retinitis pigmentosa)		AD AR XR	Reduced visual acuity, central scotoma with initially normal peripheral isopters, dyschromatopsia. Central pigment epithelium defects are first seen in the macula and later spread to cover the entire fundus. These signs are accompanied by optic atrophy, and narrowed retinal arterioles. Dark adaptation testing, perimetry (both static and kinetic), scotopic and photopic ERG, and multifocal ERG are helpful in establishing the diagnosis.	**AD:** **CORD2:** 19q13.3 **CORD5:** 17p13–p12 **CORD6:** 17p13.1 **COD3:** 6p21.1 **CRD:** 17q **CORD7:** 6q13–15 **RCD1:** 6q25–26 **AR:** 1p21–13 3q21–q24 **RDH1:** 12q13–q14 **CORD5:** 17p13–p12 **CORD8:** 1q12–q24 **CORD9:** 8p12–q11 **XR:** **RP3:** Xp21.1 **COD1:** Xp11.4 **COD2:** Xq27 **CORD3/RP15:** Xp22.13–22.11	 *CRX* *GUCY2D* *GUCA1A* *HRG4* *ABCA4* *RHO* *RDH5* *RPGR*	

Table 18.2. (*Continued*) **3. Retinal dystrophies with predominantly macular or posterior pole abnormalities**

Disorders	Frequency	Mode of inheritance	Symptoms (ocular/general)	Gene location	Gene name	Molecular genetic testing
Achromatopsia (rod monochromacy)	1:100,000	AR	Signs and symptoms commonly include reduced visual acuity, nystagmus, severe photophobia, and often high astigmatism and/or myopia.	**2q11–q12** 8q21.1–22.1 14	*CNGA3* *CNGB3*	http://www.genetests.org/ (An informational service for physicians that is funded by the National Institutes of Health)
Juvenile macular degeneration (Stargardt's disease, also fundus flavimaculatus)	1:10,000	AR Rarely AD	Marked reduction in visual acuity to 20/200 or worse, photophobia, central scotoma, dyschromatopsia, pigment dispersion in the macula (described as "hammered bronze"), frequently accompanied by the yellow flecks that give fundus flavimaculatus its name. Fluorescein angiography exposes numerous macular window defects in the pigment epithelium (a form of macular ring pattern) and marked attenuation of choroidal fluorescence, the so-called dark choroid. Multifocal ERG often helps to confirm the diagnosis.	**STGD1:** 1p22.1–21 **STGD2:** 13q34 **STGD3:** 6q14 **STGD4:** 4p	*ABCR*	I
Central areolar choroidal dystrophy (CACD)		AD AR	Circumscribed central atrophy of the choriocapillaris and the pigment epithelium exposing white-walled and obliterated choroidal vessels. There is progressive loss of visual acuity and formation of a central scotoma.	**CACD:** 17p13–12		

Table 18.2. (*Continued*) **4. Developmental defects of the optic nerve and afferent visual pathway**

Disorders	Frequency	Mode of inheritance	Symptoms (ocular/general)	Gene location	Gene name	Molecular genetic testing
Aplasia or hypoplasia of the optic nerve DeMorsier's syndrome	Uncommon	Most commonly AD Sporadic	Usually in the context of severe cranial malformation, neurologic and/or metabolic syndromes: A subset of Kallmann syndrome (hypogonadism and hypogenitalism, anosmia, variable renal agenesis, hearing loss, dyschromatopsia, poor cognitive development, and cleft palate) coupled with nasal hypoplasia and coloboma of the iris, retina, and/or choroid			http://www.genetests.org/ (An informational service for physicians that is funded by the National Institutes of Health)
Aicardi's syndrome	>100 cases described (46,XX or 47,XXX)	Most commonly XD	Chorioretinopathy and/or coloboma; agenesis or hypoplasia of the corpus callosum, neonatal tetany, myoclonus, delayed cognitive development, and microcephaly	Xp22.3		
Coloboma of the optic nerve (morning glory disc)		AD	Circumscribed, deep, developmental defect of the anterior optic nerve, sometimes accompanied by persistence of the hyaloid artery. Acuity is not usually affected, if no other deficits are present. Relative constancy of trait's appearance among sibships.	10q24.3–25.1	PAX2	
Optic nerve pit		Unknown	Usually unilateral, atypical minicoloboma of the optic disc of uncertain origin. Developmental pits or round defects of the optic disc, usually in the inferotemporal sector of the disc. Visual function of the eye is not usually affected, although leakage of fluid into the subretinal space in the posterior pole can cause a loss of acuity. Visual field defects are uncommon, and are usually no more than enlargements of the physiologic blind spot or small sectoral/arcuate deficits.			
Drusen of the optic disc		AD with reduced penetrance	Numerous, small clusters of translucent, microspherical bodies on or within the optic disc substance, sometimes associated with arcuate scotomas and/or reduced acuity. Progression is uncommon. Photography with the barrier filters for fluorescein angiography demonstrate autofluorescence. Ultrasound often confirms the diagnosis.	2p21–16		

Table 18.2. (*Continued*) **5. Hereditary optic atrophy (OA)**

Disorders	Frequency	Mode of inheritance	Symptoms (ocular/general)	Gene location	Gene name	Molecular genetic testing
Simple or congenital optic atrophy		AR	Congenital optic atrophy with severely reduced vision, achromatopsia, nystagmus, and peripheral visual field loss			http://www.genetests.org/ (An informational service for physicians that is funded by the National Institutes of Health)
Juvenile or Kjer type of optic atrophy (OPA 1)	1:50,000	AD	Later appearance of optic atrophy, usually by age 6, with a somewhat milder degree of acuity reduction (0.3–0.6), initially tritanopic dyschromatopsia, later turning to a red/green discrimination deficit with paracentral or central scotomas and optic disc pallor	**OPA1:** 3q28–q29	*OPA1*	
X-linked OA (OPA 2)	Very rare	XR	Hereditary optic atrophy that affects only male descendents, often associated with a variety of neurological symptoms	**OPA2:** Xp11.4–p11.2		
Neonatal or juvenile OA (OPA 3)	1:10,000 among eastern Mediterranean populations	AR	OA with choreiform movement disorders and spastic paraplegia	**OPA3:** 19q13.2–13.3		
OPA 4		AD	Autosomal dominant optic atrophy reported in an American family of German decent.	**OPA4:** 18q12.2–q12.3		
Leber's hereditary OA	1:50,000–100,000	MT	Initially unilateral, then bilateral subacute loss of acuity to a 20/200 level largely among males. Red-green dyschromatopsia, central, paracentral and cecocentral scotomas. Acute stage fundus appearance typically includes optic disc margin blurring and a peripapillary microangiopathy that does not leak dye during a fluorescein angiogram. Within 6 weeks the fundus appearance changes to one of optic disc pallor.	**LHON** mtDNA	Primary mutations (>95%): 11778 (*MTND4*) 3460 (*MTND1*) 14484 (*MTND6*) 15257 (*MTND6*)	
Behr-type OA	About 40 cases have been reported	AR Occasionally AD	Onset in early childhood of progressive loss of acuity without complete loss of vision with varying degrees of optic atrophy, strabismus (75%), nystagmus (50%), ataxia, poor cognitive development, and spasticity			

Chapter 19

Pediatric Neuro-Ophthalmology

B. Lorenz

Compared with the examination of adults, the neuro-ophthalmic evaluation of children differs in that there are significant developmental changes in visual and oculomotor function that limit their quantitative assessment. There are available, however, a number of qualitative and quantitative methods that, along with objective physical findings, allow for the more accurate identification and classification of neurological disorders of vision in children.

Normal Visual and General Development of Children

Neuro-ophthalmic disorders are frequently important elements or overt expressions of the CNS diseases that affect children, including neurodegenerative disorders, Hence, the age-related development of visual function must be carefully considered (■ Table 19.1). If the patient has older siblings, the parents can often provide useful comparisons between siblings in assessing their relative visual capabilities.

Practical Methods for the Neuro-Ophthalmic Evaluation of Children

In this chapter emphasis is placed on simple testing methods that can be relied on in any practice. ■ Table 19.2 provides a summary of the various ophthalmic and related consulting options for the evaluation of visual function in children. It is most important that the examiner be able to establish a relationship of trust with the patient. This begins with the pediatric waiting area. Quiet observation of the child and of the interactions between the parents and the child will yield important clues. All tests should be carefully explained in advance. The explanation should be frank and include the predictably unpleasant parts of the examination, such as the discomfort caused by mydriatic agents. It is often helpful to have the parents bring with them any occlusion device in use. Having the patch in place will allow for a peaceful period of observation, testing of acuity, and assessment of any compensatory head posture. (Monocular testing should be first with the occluding device in place, followed by removal of the occluder and binocular testing.) A number of objects of visual interest to the child, such as *Sesame Street* or cartoon characters/puppets, or other age-appropriate objects, will facilitate observation of pursuit and saccadic eye movements. Good fixation can be achieved by having the child try to "blow out" the hand light used for external examination. During the examination the more common devices used can be described as "magic glasses" or "sunglasses". Music or the mimicking of animal or automobile sounds usually encourages cooperation. Small television sets with a diagonal screen size of 5 in. (and placed 10 or more feet away) can be used to play cartoon videos, which will capture the child's attention. Prior to a more careful examination, the initial period of cooperation should be exploited to complete quickly a preliminary examination of all structures of both eyes.

Pearl

Once the examiner has developed a level of trust, essential instruments should be at hand, including a handheld slit lamp, an indirect ophthalmoscope (preferably head-mounted), a direct ophthalmoscope, and a retinoscope.

History and Neurological Assessment

For infants and small children, the history by its nature is indirect and depends on the ability of the parents or caregivers to describe accurately the visually dependent behavioral characteristics of the child. An experienced examiner can use the period of history taking to observe the child's behavior, often obtaining valid information that can guide the history-taking process. The most important elements are summarized in ■ Table 19.3. It is understood that the history taking must be done by the physician and cannot be delegated to others.

Table 19.1. Milestones of normal visual and general development

Age	Normal visual development	Motor function	Social development
After 30 weeks of gestational age	Pupillary light responses +		
At birth		Optokinetic nystagmus + with limited speed of the slow phase – nasotemporal asymmetry until 2–4 months of age	
1 month	Stable ocular positioning		
1–3 months		Good saccades	
6 weeks	Recognizes known faces	Head held steadily	Responsive smile
6–8 weeks		Good pursuit movements and steady fixation maintenance	
2–5 months	Threat induced blinking		
3 months	Visually inspects handheld objects	Holds objects	Babbles
3–7 months	Good stereopsis		
4 months	Adequate accommodation and foveal maturity		
6–8 months		Sits, turns	Expresses displeasure, holds bottle
7 months to 2 years	Myelination of optic nerves complete		
9–12 months		Crawls, stands with support, runs with hand held	Waves good-bye, speaks two to four words
12–15 months		Runs without help, throws objects, scribbles with crayons, builds stacks with wooden blocks	Points at desired objects, understands names of various objects, helps when getting dressed
18–24 months	Looks at picture books, names colors (by 2 years of age)	Stoops and picks up objects, runs, begins attending to cleanliness	Uses a spoon, speaks two- to three-word sentences, knows own body parts

Modified from Buckley EG (2003) Pediatric neuroophthalmology examination; and Stout AU, Wright KW (2003) Pediatric eye examination. In: Wright, K (ed) Pediatric ophthalmology and strabismus. Mosby, St. Louis

Table 19.2. Methods for examining children

Ophthalmic examination	Consultative examination
• History • Neurological examination • Spatial acuity • Binocular vision • Brückner test (red fundus reflex) • Pupillomotor responses • Perimetry • Color vision • Oculomotor examination • Refraction • Accommodation • Morphology: biomicroscopy and ophthalmoscopy • Electrophysiology	• Pediatric or neuropediatric • Neuroradiologic • Neurosurgical • Ear, nose, and throat • Child psychologist, psychiatrist • Human geneticist

Table 19.3. History and neurological assessment

- Course of pregnancy
- History of labor and delivery
- Family history
- Neurologic and psychomotor milestones of development
- Suspicion of brain damage? Spasticity? Seizures? Ataxia?
- Hearing problems?

Table 19.4. Assessment/measurement of vision and age-dependent testing of vision

Assessment/measurement of vision

Qualitative (Questioning of the parents is important!)
- Do you believe your child can see?
- Does your child react to lights, faces, or toys?
- Does he/she fix visual attention on your faces, on the bottle, or on own hands and feet?
- Does your child react to noises, but not to visual stimulation?
- Central fixation? Searching fixation? Corrective head posture
- Does your child pursue moving objects with his/her eyes?

Quantitative
- Binocular testing first, while child is relatively undisturbed (Build trust!)
  - With manifest or latent nystagmus the binocular visual acuity is often better
- Then monocular testing of acuity
  - Ideally with an occlusion patch – in the event of latent nystagmus fogging of distance vision or use of stereoptic isolation helps
- When possible, measure near acuity
  - It is often better than distant acuity (e.g., when nystagmus is present – important for questions about schooling)
- Optokinetic nystagmus (OKN)
  - When horizontal and vertical responses are elicitable, useful visual function can be expected
  - When not elicitable no useful conclusion can be made

Age-dependent testing of vision

Age	Expected acuity	Tests for when age-appropriate general development is present	Tests for when there is delayed psychomotor development
<2 months	0.1–0.3	Observe: blinking at bright lights, fixation and pursuit of objects (faces!), OKN	Observe: blinking at bright lights, fixation and pursuit of objects (faces!), OKN
2–6 months	0.4	Observe: blink response to visual threat, reaching for objects, PL (TAC), OKN, *VEP*	Observe: blink response to visual threat, reaching for objects, PL (TAC), OKN, *VEP*
6–18 months	≥0.5	PL (TAC, Cardiff-Cards), OKN, *VEP*	Observe: blinks at visual threats – fixes and follows objects (faces!) PL (TAC, Cardiff Cards), OKN, *VEP*
18–36 months	≥0.6	PL (Cardiff Cards), LEA-Test *VEP*	PL (TAC, Cardiff Cards), OKN, *VEP* Reaches for small, hard candy spheres (1 mm to 1 cm in size)
3–5 years	≥0.6	Tumbling Es, Landolt rings, Lea test *VEP (and mfERG) when functional visual loss is suspected*	PL (TAC, Cardiff Cards), *VEP* Reaches for small, hard candy spheres (1 mm to 1 cm in size)
≥6 years	≥0.8	Letters, Landolt rings *VEP and mfERG (when functional visual loss is suspected*	PL (TAC, Cardiff Cards), OKN, *VEP*, Lea test Reaches for small, hard candy spheres (1 mm to 1 cm in size)

Tests written in italics are those of lower or limited use
When using the Cardiff-Cards, one will commonly find an overestimation of acuity
TAC Teller Acuity Cards, *OKN* optokinetic nystagmus, *VEP* visually evoked potentials, *PL* preferential looking, *mfERG* multifocal ERG

Visual Testing

The important elements of pediatric vision testing are listed in ■ Table 19.4, and ■ Table 19.5 and provide a summary of the most appropriate methods, based on the child's age or level of development.

Preferential-looking methods are now established as conventional tests. Teller Acuity Cards (TAC) measure spatial acuity by grating resolution. In children with strabismic amblyopia, this method can produce an overestimate of function. In addition, the grating acuity cannot be reliably transposed into a Snellen acuity level. Grating test object methods measure a recognition function that is not strictly comparable with the results of conventional spatial acuity testing. For older children, the Cardiff Cards have proven to be effective (■ Fig. 19.1 a). Testing with sequential rows of alphabetical characters, e.g., the C chart according to Haase or the Lea character sequence cards (■ Fig. 19.1 b) allows for a distinction between acuity reductions because of a microstrabismus on the one hand, and a developmental central scotoma caused by diseases in the retrobulbar visual pathways on the other. This is because of the crowding phenomenon, which causes acuity levels for identification of single optotypes to be significantly better than those obtained by testing with rows of letters.

Reliable results, when testing children's visual function, require the use of trained personnel who are familiar with the specific techniques suited to the neuro-ophthalmic examination of children.

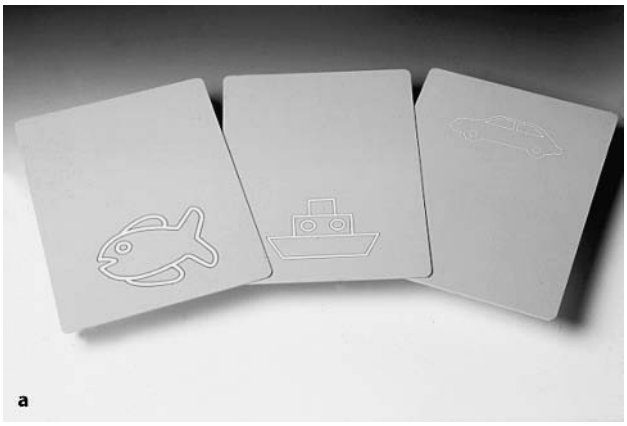
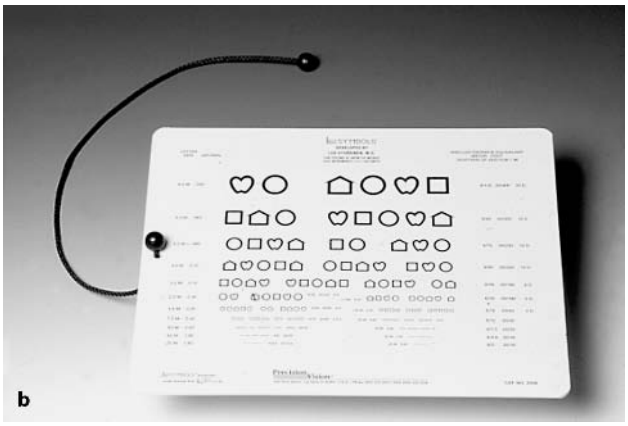


Fig. 19.1. a Acuity testing of small children. Cardiff Cards. The vertical orientation of the test characters has the advantage that the results will not be affected by horizontal but by vertical, motility disturbances. Visual function may be overestimated by this method, but it allows for a valid determination of interocular differences in preverbal children in whom the Teller Acuity Cards have already become uninteresting (i.e., from about 12 to 18 months of age).



b Vision tests for small children. Starting at about 24 months of age, comparison tests become useful. The Lea test has proven itself effective for both distant and near testing, including measures of the crowding phenomenon. Thus, it is useful for differentiating strabismic amblyopia on one hand from an acuity loss caused by an optic neuropathy on the other

Only specifically trained technical personnel should be permitted to record visual acuities. They must have specific knowledge of neuro-ophthalmic disorders and of the methods of testing suited to the examination of children.

Pupillomotor Testing

The testing of pupillary motility (see Chap. 5) is mandatory but is often neglected. The following discussion covers a few of the unique aspects of pupillary testing in children.

It is particularly easy to miss a strictly (or very strongly) unilateral loss of afferent function. The swinging flashlight test is difficult to use with children, particularly those with darkly pigmented irises. As an alternative to the swinging flashlight test, one can use monocular occlusion. The eye with an afferent deficit will show pupillary dilation ("escape") when the contralateral eye is occluded. The parents can help in such cases when specifically asked, by confirming that during patching of the dominant eye, the pupil of the strabismic eye is consistently and strikingly larger than when both eyes are open. (A typical example is the unrecognized optic disc hypoplasia of the strabismic eye).

A manifest anisocoria is not produced by a relative afferent pupillary defect, but rather reflects an efferent (autonomic) motor deficit.

! Note

Among newborns the distinction between essential anisocoria and Horner's syndrome is particularly important. Absence of sympathetic supply to the iris is frequently associated with mediastinal disease, such as in infants with neuroblastomas. Thus, Horner's syndrome requires an identification of the cause of the sympathetic deficit before it is dismissed as unimportant.

Nevertheless, even with thorough study, in only about 20% of cases of infantile Horner's syndrome will the exact cause be found. When a Horner's syndrome appears in the first few months of life, a typical heterochromia iridis will eventually appear. Initially, the irides will have identical color. But, since the development of iris stromal pigmentation requires the presence of an intact sympathetic supply, an easily apparent difference in iris color will appear by age 2 (■ Fig. 19.2).

Bilaterally absent or very poor pupillary light responses in an otherwise seemingly healthy infant most frequently indicate Leber's congenital amaurosis. This should be distinguished from delayed maturation of the pupillomotor pathways in which the pupillary light responses may be slow but are preserved.

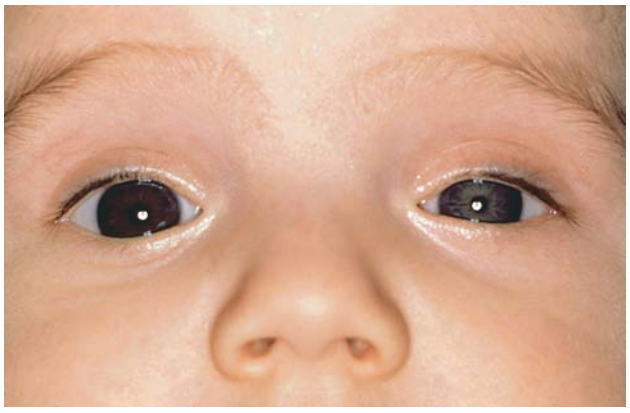


Fig. 19.2. Early childhood Horner's syndrome in the left eye with evident heterochromia iridis and miosis. Heterochromia is a reliable sign of an infantile onset

Visual Field Testing

A precise measure of visual field function in infants and toddlers is not possible. However, neuro-ophthalmically relevant defects are homonymous or bitemporal hemianopias, marked altitudinal deficits, or sector defects. Profound defects of this sort can usually be detected with a modified type of confrontational visual field testing. A summary is provided in ■ Table 19.5. ■ Figure 19.3 illustrates the preferred method for use with infants and also the procedure intended for use with somewhat older children.

Color Vision Testing

For testing color vision in preschool children, the Matsubara Color Vision Test (Handaya Co., Ltd., Tokyo) and the Color Vision Made Easy test by T.L. Waggoner (1994) have proved to be useful. In a modification analogous to the form comparison method (Lea test), black-and-white copies can be used for comparison.

Oculomotor Testing

When testing oculomotor function in small children, including pursuit and saccadic movements (see Chap. 11), the use of attractive toys, such as finger puppets, blinking colored lights, or small sound makers, has proved helpful.

Vestibuloocular Reflexes

When testing vestibuloocular reflexes (VOR) and their suppression in infants, it is best to hold the child in both hands with the arms extended, and then to turn to the right or left, while observing the child's eye movements (■ Fig. 19.4 a).

When testing the so-called doll's eye phenomenon, the child's head is moved while the body is held in a fixed position. This is easily done for horizontal movements, but is difficult for vertical movements. Vertical manipulation of the head often results in a loss of the child's cooperation (■ Fig. 19.4 b).

A detailed discussion of the testing of optokinetic nystagmus and the differential diagnosis of ocular motility disorders can be found in Chaps. 10 and 11.

Table 19.5. Visual field testing of children

	Test	Comments
6 months to 2 years	Central fixation on an attractive stimulus, while introducing objects in the periphery, moving from unseeing to seeing	An assistant introduces the object from the periphery, while the examiner carefully monitors the child's responses
>2 years	Finger play	One finger, five fingers, fist, fixation in abduction[a], monocular testing
>3 years	Finger counting	(One, two, five fingers, or fist) Monocular and binocular testing, altitudinal defects can also be discovered
Over 6–7 years	Goldmann (kinetic)	Look out for false constriction – test first with confrontation
From 8 to 10 years	Kinetic and static testing	Reproducible findings increase validity

[a] If fixation in abduction can be maintained, the eye will be restricted from further movement to the temporal side, increasing the accuracy when testing the temporal visual field. This trick is not of help with the nasal hemifield, since the nose often obstructs the nasal hemifield

Fig. 19.3. a, b Visual field testing of infants. A useful method is to have an associate introduce an interesting object starting in the far periphery and move toward the center of the visual field. Hemianopic defects can be demonstrated, including both horizontal and vertical hemianopias. **c** Visual field testing for preschool children. Kindergartners should be asked to hold up the same number of fingers as the examiner does. Somewhat older children can be asked to describe the number of visible fingers

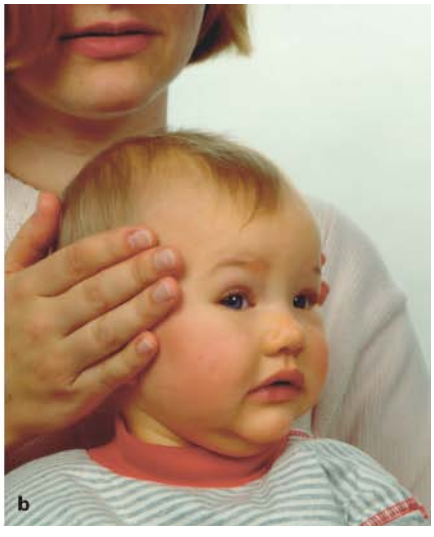


Fig. 19.4. a Testing of the vestibulo-ocular reflexes. Both simple and effective is the technique of holding the infant with both hands at arm's length, while turning about to one side or the other. The rate of turning must be sufficiently fast that it precludes fixation on objects in the surrounding area, otherwise the examiner will be generating an optokinetic nystagmus, rather than a vestibulo-ocular nystagmus. **b** Testing of the vestibulo-ocular reflexes. Testing with the doll's eye phenomenon is only poorly effective, as it usually generates defensive responses and unhappiness

Table 19.6. Ocular causes of a corrective head posture (CHP)

Maintaining binocularity
• With nonconcomitant forms of strabismus – Monocular strabismic hyperdeviation (head-tilt test – Bielschowsky positive) – A or V pattern – Duane's syndrome – Brown's syndrome – Paralytic strabismus • With monocular or binocular ptosis
Maximizing acuity
• Nystagmus with a null position outside of the primary position • Upper lid ptosis (so-called posture of obligatory arrogance) • Gaze paresis
Head posture of infantile strabismus

Corrective Head Posture

When an unusual and involuntary head posture is present, one should determine first whether it is an ocular form of corrective head posture (CHP). ■ Table 19.6 summarizes the most important causes of ocular CHP. Correct recognition of an ocular form of CHP is important, so that unnecessary physiotherapeutic or orthopedic treatments can be avoided. Spontaneous remission of CHP can sometimes be an indication of a worsening of vision, as in the loss of binocular vision. Proper classification of CHP requires both monocular and binocular testing. CHP is to be distinguished from a faulty head posture that has no apparent visual source, particularly when evaluating children with infantile strabismus.

Refraction

Even in this age of automated refractometry, determination of refractive errors in infants and children is usually best done by experienced examiners, using retinoscopy and cycloplegia. For children with nystagmus, retinoscopy is the only effective method for measuring refractive errors.

Measurement of Accommodation

An estimation of accommodative amplitude, when examining small and uncooperative children, is usually best done with the retinoscope. When possible, this should be done following spectacle correction of ametropia. A small fixation object that can attract the child's attention is affixed to the front of the retinoscope, just below the optical axis of the instrument. If brief illumination of the retinoscope attracts the child's visual attention, fixation will stimulate accommodation, so that the neutral fundus reflex (neutralization point) of emmetropia will be seen at all distances between the eye and the retinoscope. Estimation of accommodative amplitude is especially important in children with cerebral damage, particularly those with a history of prematurity and developmental delay, so that proper glasses can be fitted with bifocal segments, or so that monofocal glasses for near vision use can be given to infants. This is particularly important for visual imprinting of maternal facial features and bonding between mother and infant. Also, measures of accommodative amplitude can explain the child's rejection of corrective lenses, such as when a full correction of myopia has been prescribed.

Peculiarities of the Ocular Examination in Children

Features of the ophthalmic examination in small children can often indicate the source of an afferent visual disturbance. Optic atrophy, papilledema, and congenital optic disc anomalies must be ruled out.

Optic Atrophy

If optic atrophy is found, the differential diagnosis that one must consider is very extensive. When retinal or hereditary causes have been ruled out, a neuroradiologic examination is necessary. The flow diagram in ■ Fig. 19.5 summarizes the potential sources of optic nerve damage. A characteristic form of atrophy is found in lesions of the optic tract (■ Fig. 19.6; see also Chap. 8, ■ Fig. 8.23). Tract lesions in children appear not only from damage to the postchiasmal portions of the third-order neurons (retinal ganglion cell axons), but also are found associated with damage to the fourth-order neurons that form the postgeniculate optic radiations and their terminals in the primary visual cortex. This is true when the damage dates from the period of intrauterine development or during the first few months of life (at most 3 to 6 months of age). The mechanism is thought to be a retrograde trans-synaptic degeneration in which faulty development of geniculate ganglion cells provides no useful termination for the retinal ganglion cell axons, resulting in optic atrophy.

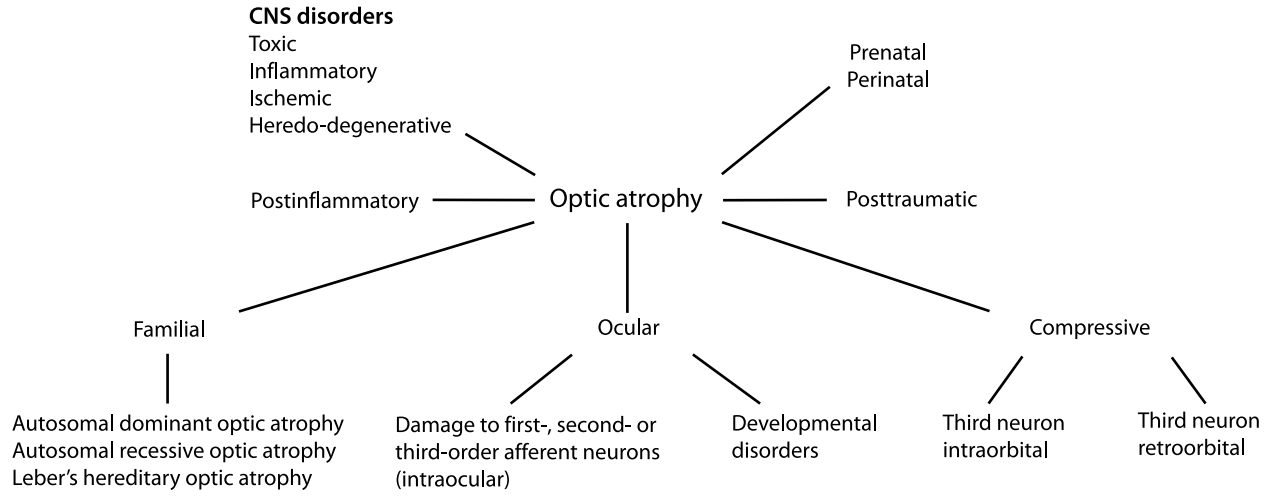
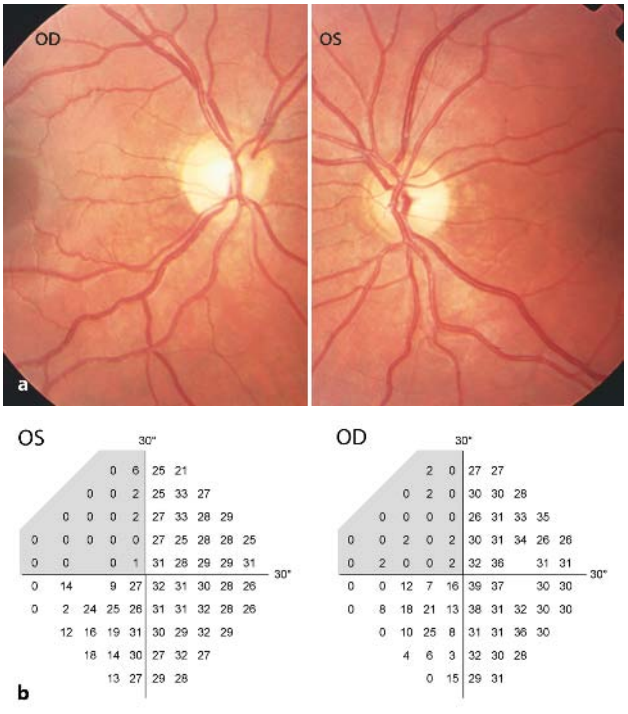


Fig. 19.5. The differential diagnosis of optic atrophy in children



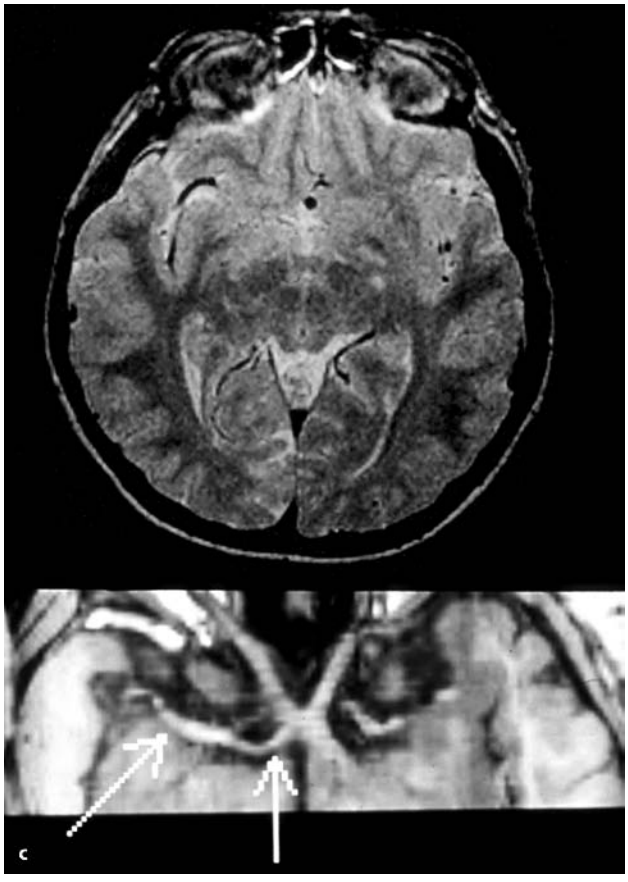


Fig. 19.6. **a** Lesion of the right optic tract with an incongruous, homonymous quadrantic hemianopia to the left. Optic discs: The disc of the right eye has temporal pallor with a shallow excavation, while the disc of the left eye has a bow-tie pattern of pallor, evident in both the nasal and temporal disc quadrants. This finding is easily missed, when a direct ophthalmoscope is not used. **b** Visual field testing (static perimetry with the Humphrey Field Analyzer), of the central visual field, i.e., within 30° of eccentricity. **c** MRI. Shown is the case of an 11-year-old patient with a circumscribed cortical lesion (zone of ischemia) and associated degeneration of the retrogeniculate optic radiations and optic tract on the right side. This finding reliably marks the damage as having been either intrauterine or neonatal in origin. Family members reported that the child could not catch a ball approaching from the left side. The *vertical arrow* indicates the tract hypoplasia; the *left arrow* indicates the middle cerebral artery

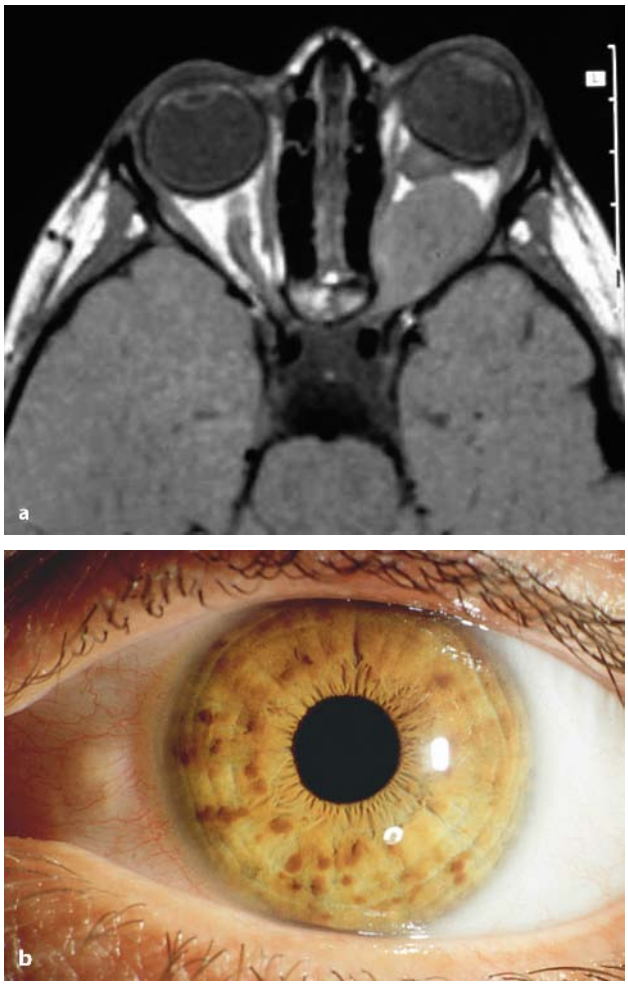


Fig. 19.7. a Optic nerve glioma (MRI). It is important to note that the nerve itself is enlarged, in contrast to the appearance of an optic sheath meningioma. Kinking or sharp angulation of the optic nerve is also very characteristic. Gliomas of the optic nerve frequently occur in the setting of neurofibromatosis type 1 (NF1). Depending on the location of the tumor, optic disc swelling may be seen at the time of discovery. In later stages, a partial or complete optic atrophy will be apparent. **b** Lisch nodules are typical in NF1, but may not be apparent during childhood

Optic Disc Elevation

The differential diagnosis of optic disc elevation in children includes several specific entities. A more detailed discussion of the various etiologic sources of disc elevation, independent of the patient's age, can be found in Chap. 8.

Optic Disc Drusen

During childhood, drusen are not usually calcified, making their identification difficult. Echographic detection of drusen is simple and noninvasive, when the drusen are calcified, and visible drusen are autofluorescent, providing a simple verification of the diagnosis. Superficially located drusen are easily identified by direct ophthalmoscopy, and they have an unmistakable appearance. It is often helpful to examine multiple members of the patient's family, since drusen develop as an autosomal dominant trait. They can also be found linked to a number of hereditary retinal degenerations.

Optic Nerve Gliomas

Optic nerve gliomas (■ Fig. 19.7 a) frequently occur in the setting of neurofibromatosis type 1 (NF1). Common signs and symptoms of NF1 include café-au-lait spots in the skin (at least six light brown, well-demarcated, macular skin marks) and Lisch nodules (pigmented iris hamartomas, consisting of epithelioid cells of neurectodermal origin; ■ Fig. 19.7 b), although they do not necessarily present during childhood. Lisch nodules are almost always absent in infants, are present in 50% of cases by age 5 years, and in 90% by age 20 years. NF1 is inherited as an autosomal dominant trait, and the spontaneous mutation rate is high.

Optic Nerve Sheath Meningioma

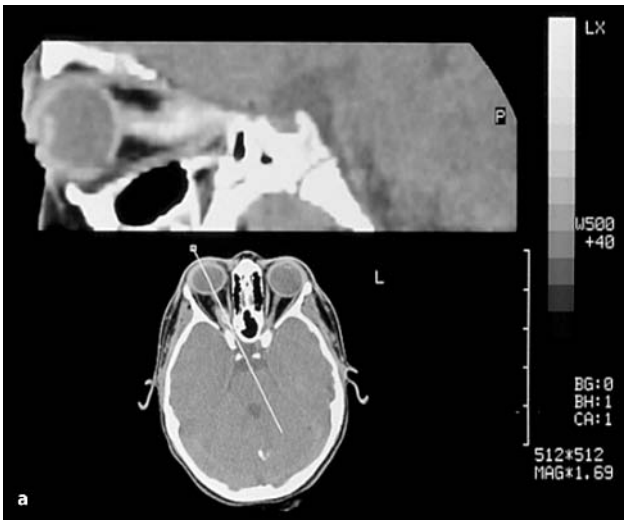
Disc elevation (infrequently) can be the presenting finding of an optic nerve sheath meningioma in children (■ Fig. 19.8 a). Neuroradiologic imaging almost always allows a clear and decisive differentiation between optic nerve gliomas and sheath meningiomas. Sheath meningiomas frequently occur in patients with neurofibromatosis type 2 (NF2), which is inherited as an autosomal dominant trait. NF2 commonly presents as an acoustic neuroma and is not infrequently bilateral. Initial findings can also include retinal pigment epithelial hamartomas (■ Fig. 19.8 c) and a variety of lens opacities (■ Fig. 19.8 b).

Craniosynostoses

Premature or disordered closure of cranial sutures can present as optic nerve compression, with or without optic disc edema. Visually evoked potential (VEP) testing and ophthalmoscopy are frequently helpful in determining a correct diagnosis.

! Note

Absence of optic disc edema does not rule out a compressive lesion of the optic nerve, as for instance in children presenting with open fontanels or already established optic atrophy.



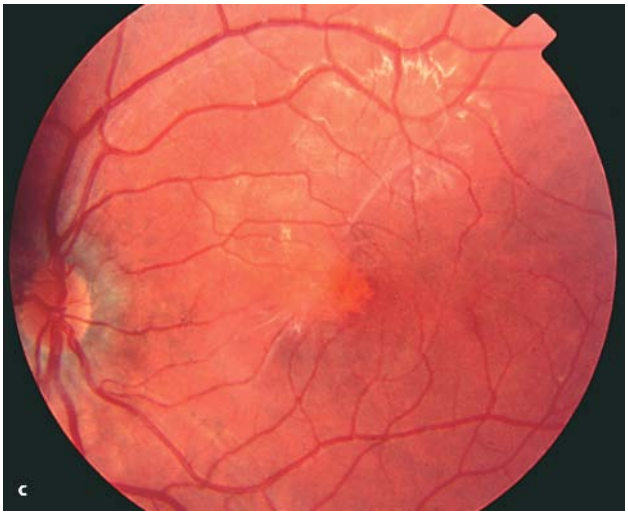


Fig. 19.8. **a** Optic nerve sheath meningioma (CT scan). The optic nerve itself has not changed, but it has been surrounded by tumor. Calcification of the tumor is a very characteristic sign, and best visualized with CT scan. Calcification may be absent in particular in larger tumors. Depending on the location of the tumor, optic disc swelling may be seen. Optic nerve sheath meningiomas also occur in the context of neurofibromatosis type 2 (NF2). **b** Additional ocular findings in NF2 include unilateral lens opacities, e.g., lens fiber haziness. **c** Retinal pigment epithelial hamartoma in a patient with NF2. These hamartomas may also occur as an isolated finding

Congenital Optic Disc Anomalies

■ Table 19.7 provides a summary of congenital optic disc anomalies (see Chap. 8). It is important to recognize that the appearance of the anomaly gives no absolute indication of the visual potential of the eye. The swinging flashlight test is of help in identifying anomalies associated with severe impairment of visual potential. But if there is any doubt about the visual potential of such an eye, a trial of occlusion therapy should always be attempted, so as to minimize the risk of amblyopia.

Table 19.7. Developmental anomalies of the optic disc

Optic nerve hypoplasia
Morning-glory optic disc anomaly
Optic disc coloboma
Peripapillary staphyloma
Megalopapilla
Optic nerve pit
Tilted disc

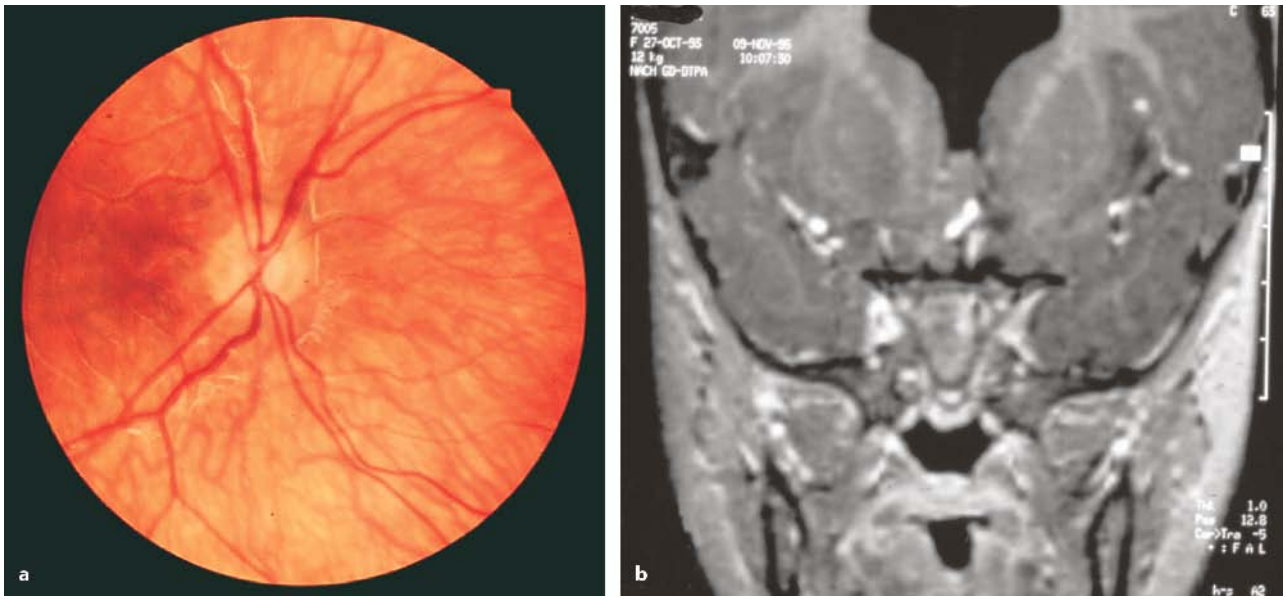


Fig. 19.9. a Optic disc hypoplasia. The peripapillary scleral ring (the so-called double-ring sign) can easily be missed and the outer ring mistaken for the true disc margin. This mistake is easily made when examining uncooperative children. **b** A missing septum pellucidum as the minimal necessary sign of an associated midline defect, as in De Morsier's syndrome, also called septo-optic dysplasia

Optic Disc Hypoplasia

Hypoplasia of the optic disc commonly goes undetected in unruly children seen by inexperienced examiners. At first glance, the typical peripapillary scleral ring may easily be mistaken for the margin of the disc (■ Fig. 19.9). Hypoplasia (and disc colobomas, see below) can be associated with midline developmental defects. In its most limited form, this will be expressed as only an absence of the septum pellucidum. Of more functional importance is an associated hypothalamic hypoplasia. Growth retardation is usually associated with a deficiency of somatotropin, hypothyroidism, or an adrenocorticotrophic hormone (ACTH) deficiency. A deficiency of ACTH release is particularly problematic during periods of stress, as in the face of a febrile disease, which can lead to convulsive seizures. The treatment of choice is not the use of anticonvulsive drugs, but rather of corticosteroids. When untreated, an ACTH deficiency is potentially fatal. Children with midline defects must consequently be monitored regularly to ensure that they do not suffer from an endocrinologic deficit.

Optic Nerve Colobomas

Optic disc colobomas may occur as isolated findings, or as part of a larger constellation of several colobomatous defects that result from a failure of optic cleft closure during embryonic development. They can also be found in the company of midline defects. Recently, a hereditary association has been found between optic disc colobomas and renal hypoplasia with mutations in the *PAX2* gene.

! Note

Children with newly discovered optic disc colobomas should be carefully studied to rule out an associated renal insufficiency.

Aicardi Syndrome

In Aicardi syndrome chorioretinal lacunas result in a characteristic appearance (■ Fig. 19.10). This disorder results in such severe malformations in males, that with few exceptions, none are born living. In affected girls, malformations of the CNS present, such as agenesis of the corpus callosum, schizencephaly (a variably pronounced cleft formation of the cerebrum), and heterotopia of gray matter – a combination that can result in severe CNS seizures.

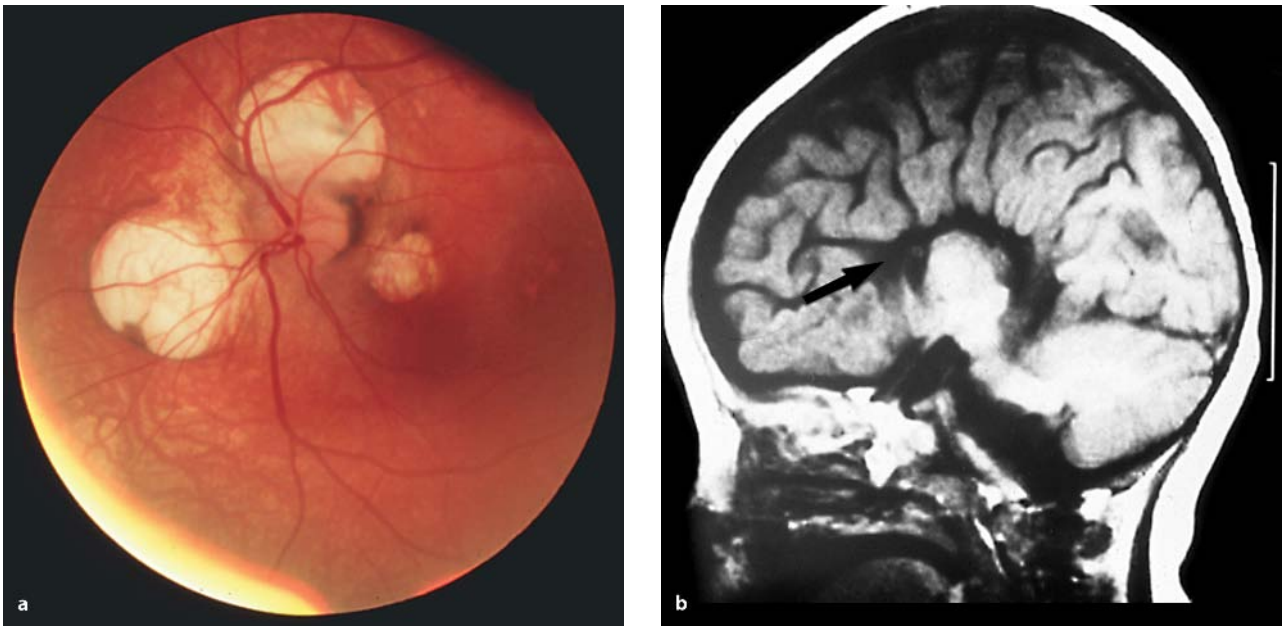


Fig. 19.10. **a** Aicardi syndrome. Circumpapillary chorioretinal lacunae in a young girl. The disease is lethal in males. **b** Aicardi syndrome. Hypoplasia of the corpus callosum (arrow) and cortical heterotopia

Nystagmus in Childhood

Congenital/Neonatal Nystagmus

Proper diagnostic classification of congenital or neonatal nystagmus is challenging. A practical schema is illustrated in the flow diagram of ■ Fig. 19.11 (see also Chap. 11).

Sensory defect nystagmus (SDN), or ocular nystagmus that arises from a congenital defect in retinal and/or optic nerve development, is in 80% of all cases considerably more common than congenital idiopathic nystagmus, which is a diagnosis of exclusion. A precise diagnostic classification allows for an accurate prognosis and assessment of the risk of recurrence in subsequent children by the same parents. Both forms can have characteristics that allow exclusion of more widespread neurological disease. Only if these characteristics are identifiable can either of the two be correctly diagnosed. When findings are uncharacteristic, complete neuropediatric and neuroradiologic examinations are required. This also holds true when complex combinations of nystagmus and other neurological disorders are mixed.

■ Table 19.9 summarizes the most frequently found disorders in children with SDN (ocular nystagmus). A form of albinism is found in more than one third of cases.

Table 19.9. The most common causes of SDN or ocular nystagmus, based on heredofamilial diseases of the retina or optic nerve

Disorders with macular hypoplasia • Albinism (all forms) • Aniridia (also minimal variants with limited iris changes) • Isolated macular hypoplasia
Cone dystrophies • Progressive cone (cone/rod) dystrophies – Leber's congenital amaurosis (LCA) (various forms) – Early onset retinitis pigmentosa • Stationary cone disease – Achromatopsia (autosomal recessive, various forms) – Blue-cone monochromacy (X-linked)
X-linked congenital stationary night blindness (CSNB) • Incomplete form (CSNB2) • Complete form (CSNB1)
Optic disc hypoplasia
Fundus colobomata
Familial isolated nystagmus (autosomal-dominant and X-linked forms)

Spasmus Nutans

See Chap. 11.

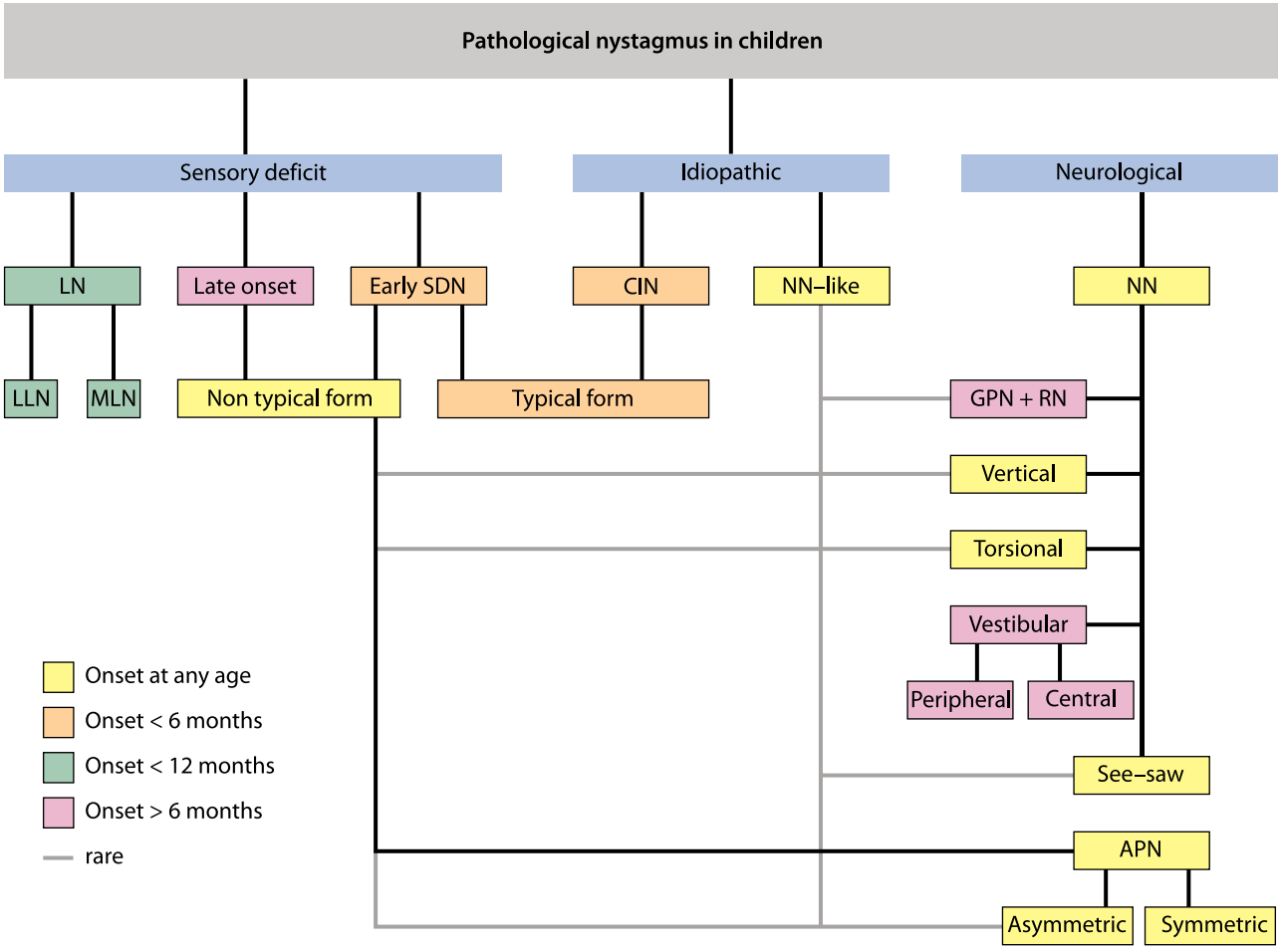


Fig. 19.11. Pathologic nystagmus in children. The flow diagram has been modified from that used by C. Harris. *APN* acquired pendular nystagmus, *CIN* congenital idiopathic nystagmus, *GPN* gaze paretic nystagmus, *LN* latent nystagmus (*MLN* manifest LN, *LLN* latent LN), *NN* neurological nystagmus, *RN* rebound nystagmus, *SDN* sensory deficit nystagmus. Published in D. Taylor's textbook *Paediatric Ophthalmology* (see "Further Reading")

Cerebral Disorders of Vision in Children

Definition

Cerebral disturbances of vision are impairments of vision caused by intracranial damage to the afferent visual pathways up to the level of the primary visual cortex. They can be found only by use of neuroradiological examination.

A cerebral disturbance of vision with an unremarkable fundus appearance is a certifying sign of intracranial disease affecting the afferent visual pathways up to the level of the visual cortex. This definition is important in some countries, since any specific claim for compensation based on visual loss requires confirmation of this sort of intracranial disease. ■ Table 19.10 provides a summary view of the etiologies of cerebral disorders of vision in children.

Table 19.10. Cerebral causes of visual damage in childhood (excluding tumors)

Common causes
• Infections of the central nervous system
• Intentional cranial trauma in child abuse, marked by fundus hemorrhages
• Hydrocephalus
• Hypoxic/ischemic encephalopathy
• Following brain hemorrhages (e.g., in prematurity)
Uncommon causes
• Secondary to a status epilepticus
• Subacute, sclerosing leukoencephalopathy
• Uremia
• Hypoglycemia
• Carbon monoxide poisoning

Table 19.11. Neuroradiologic signs associated with cerebral causes of visual damage (excluding tumors)

Periventricular leukomalacia
Infarcts in the parieto-occipital region
Infarcts in the occipital lobes

■ Table 19.11 lists the typical neuroradiologic findings in such cases. If the damage is present at birth, or appears in the first 3 to 6 months of life, fundus changes such as optic disc atrophy or pathological cupping will often be present, caused by descending transsynaptic degeneration.

Periventricular Leukomalacia

Definition

Periventricular leukomalacia is a softening of the white matter in the regions surrounding the ventricles of the brain.

Radiologically demonstrable periventricular leukomalacia is an important sign of cerebral damage in premature infants and those suffering from perinatal cerebral asphyxia. It can present with optic disc cupping that should be distinguished from the sort caused by congenital glaucoma. Associated disturbances of vision can escape detection when only spatial acuity is tested, since acuities can be largely normal in the face of significant visual loss. Other problems associated with damage to visually associated regions of cerebral cortex become apparent only later, when learning disabilities are exposed in primary school–aged children.

Congenital Brain Tumors and Other Lesions

Ocular manifestations of congenital CNS diseases can also be found, attributable to disturbances of cellular induction, migration, and proliferation. Other congenital anomalies of the brainstem and cerebellum often accompany these disorders, as summarized in ■ Table 19.12. In addition, a variety of brain tumors lead to ocular symptoms. A detailed discussion of congenital intracranial tumors is beyond the scope of this chapter, but it is dealt with more completely in Chap. 12. In all such cases the neuroradiologic findings are conclusive.

Table 19.12. Congenital brain lesions with ocular manifestations (excluding tumors)

Disorders of induction • Arnold-Chiari malformation • Holoprosencephaly • Septooptic dysplasia
Disorders of cell migration and proliferation • Fetal alcohol syndrome • Fetal hydantoin syndrome • Phacomatoses • Lissencephaly (agenesis of cerebral gyri) • Microcephaly
Other congenital anomalies of the brainstem and cerebellum • Moebius' syndrome • Joubert's syndrome • Dandy-Walker cysts
Hydrocephalus

Delayed Visual Maturation

Delayed visual maturation can occur as an isolated entity. Typically such children are noted at an age of 2 to 3 months to behave as blind, and yet seem to have normal pupillary light responses. (A differential diagnosis should include Leber's congenital amaurosis [LCA], which can be confirmed by absent or severely impaired pupillary light reactions and an undetectable or severely reduced electroretinogram [ERG].) Often, a response of the child to facial appearances may be present when light responses seem to be absent. By the age of 6 months this feature will typically become inapparent. Neither morphological nor electrophysiologic studies will show any detectable disease. Delayed visual maturation can also occur in company with retinal or intracranial diseases.

Differential Diagnosis of Unexplained Visual Loss – Psychogenic Disturbances of Vision (Functional Visual Loss)

Unexplained acquired visual loss in children can result from macular diseases that at first escape detection. This is particularly true in the early stages of Stargardt's disease. Typically, a psychogenic cause is suspected during the early stages of discovery. The diagnosis is often made by multifocal ERG (or by pattern ERG), and more recently by the detection of increased fundus autofluorescence at a wavelength of 488 nm. Correct diagnosis of an X-linked retinoschisis can be particularly difficult when only macular

changes are present. Only with precise optical examinations can schisis be found. This ordinarily requires the use of optical coherence tomography (OCT). Electrophysiology (see Chap. 7) can confirm the diagnosis.

Migraine equivalents produce the most highly varied forms of visual hallucinations, and can often be early signs of cerebral diseases that can be found only by appropriate neuroradiologic study. Psychogenic (functional) disorders of vision often pose serious problems with differential diagnosis (see Chap. 15). They constitute a diagnosis by exclusion. A high level of suspicion of a psychogenic disturbance should accompany findings, such as highly variable visual responses – as reflected, for instance, in the spiraling of isopters plotted during kinetic perimetry. If a profound unilateral loss of vision is claimed, conflicting data such as normal stereoacuity, absence of a relative afferent pupillary defect, or intact acuity demonstrated with polarizing filter isolation of test characters to one eye or the other during binocular reading usually permits a decisive determination of the psychogenic character of the visual loss.

Pearl

It is important to remember that such problems are almost never because of conscious simulation on the child's part, but are rather the byproduct of some unresolved difficulty.

Conclusion

Neuro-ophthalmic diseases during childhood include both a number of age-independent diseases and a variety of specific disorders that are variably expressed in an age-dependent fashion. Neuro-ophthalmic investigation of children with unexplained visual disorders requires the use of methods that are appropriate to the study of children, with consideration given to age-corrected measures of function. A decisive neuro-ophthalmic investigation often provides important insights into childhood diseases, facilitating their management by physicians in other branches of pediatric medicine.

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Chapter 20

Neuroradiologic Imaging

U. Ernemann and T. Nägele

It is the intended purpose of this chapter to provide the practicing ophthalmologist with an understanding of the indications for neuroradiologic procedures, and to illustrate the various imaging methods with typical examples and descriptions of their findings.

Conventional Radiologic Diagnosis

The use of conventional radiologic imaging in ophthalmology has been reduced to its role in the detection of metallic foreign bodies; for a more detailed study of soft tissues, tomographic images have completely replaced them.

Tomographic Imaging

Knowledge of the anatomic planes in which the results are depicted is a primary requirement for understanding the use of modern tomographic imaging techniques. The three principal tomographic planes are orthogonally arranged as depicted in ■ Fig. 20.1: The coronal and sagittal planes are oriented along the same planes defined by the skull sutures of the same names. (The plane of the sagittal suture bisects the two halves of the skull, while the coronal suture lies in the dividing plane between the frontal and parietal bones). The transaxial plane is orthogonal to the first two and lies athwart the long axis of the body in an orientation described as "parallel to the hat brim."

Computed Tomography

Definition

Computed tomography (CT) is a digital tomographic procedure in which beams of X-rays pass through the tissue being examined, and an anatomical image of the plane being examined is reconstructed by means of computations that start with the measured variations in tissue absorption of the energy. Multiple, evenly spaced, parallel beams form single sets that are then repeated at regularly varying rotational orientations, viewing the body through many sets for each tomographic plane being imaged. Complex matrix calculations are then used to derive highly resolved values for the radiodensity maps in each cross-sectional layer.

Indications for CT

Cross sectional tomograms for transaxial orbital CT are best when parallel to the plane of the optic nerves (■ Fig. 20.1), with a thickness of 1 to 3 mm.

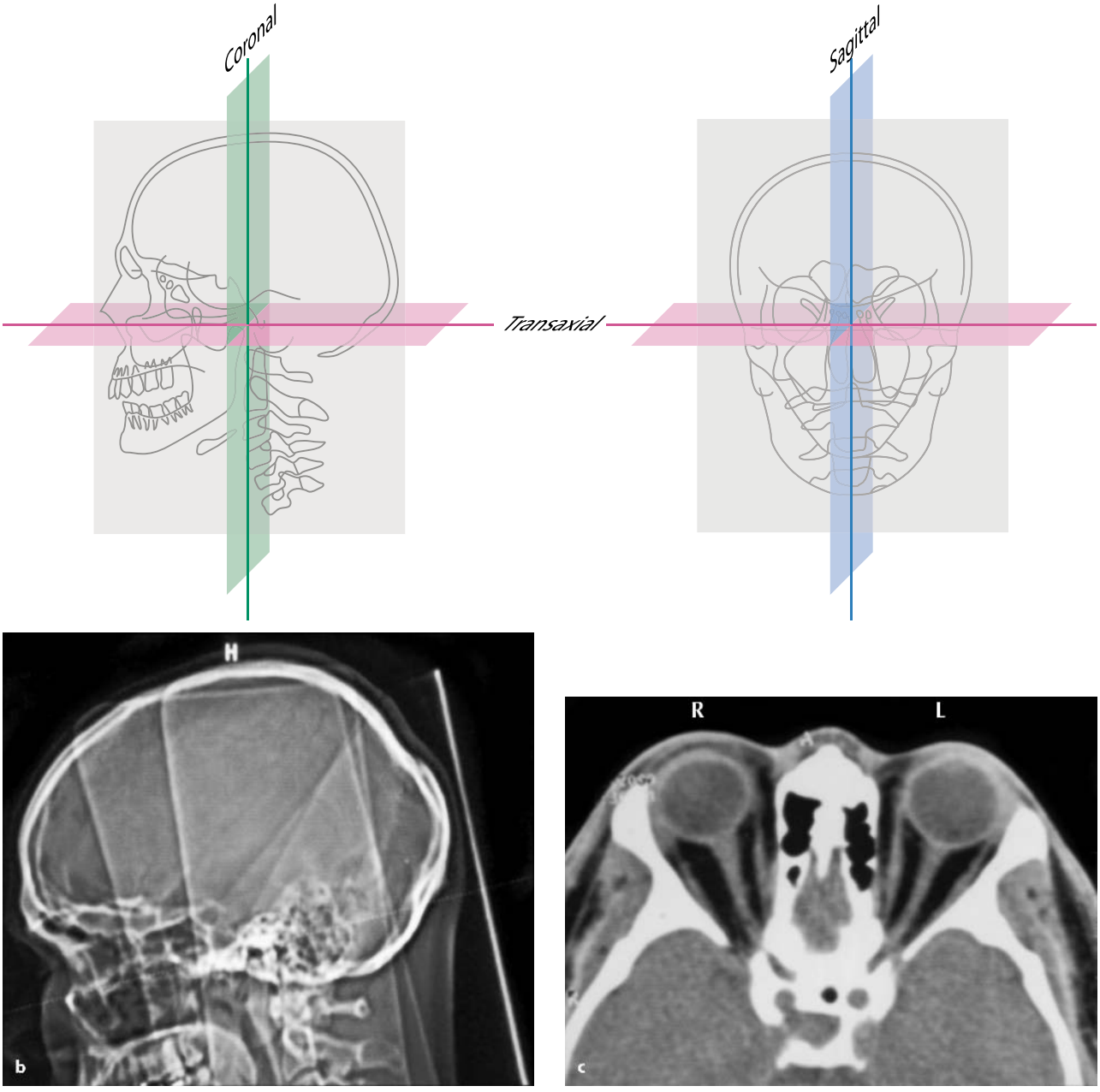


Fig 20.1. **a** Overview of the tomographic planes used in computed tomography (CT). **b** Normal findings in an orbital CT scan: topographic image showing the orientation of a tomographic plane of examination that is parallel to the optic nerves. **c** Normal findings in an orbital CT scan, transaxial plane showing both optic nerves

The various tissue density levels are assigned values (expressed as Hounsfield units [HF]) on a grayscale, and are displayed on an analog, or digital, video monitor. Air has a value of about –1,000 HF; fat has a value of about –60 HF; hemorrhages about +70 HF; and bones, +1,000 HF. By choosing appropriate data values collected from the scan and arranging them according to their density values, images can be displayed in a variety of windows (ranges of density values), some ideal for studying bone (■ Fig. 20.2 a), others for soft tissues (■ Fig. 20.2 b).

A coronal plane of scanning is ideal, when examining the orbital bones, the paranasal sinuses, and/or the extraocular muscles (■ Fig. 20.3). However, patient positioning for coronal scans has the distinct disadvantage of requiring a prone position with the head fully extended (■ Fig. 20.3 a), which is impossible for those with arthritic or mechanically unstable cervical vertebrae. In addition, metallic dental fillings produce strong artifacts that can obscure the regions of interest, since the coronal plane crosses the levels of the maxilla and mandible. For those with supple necks

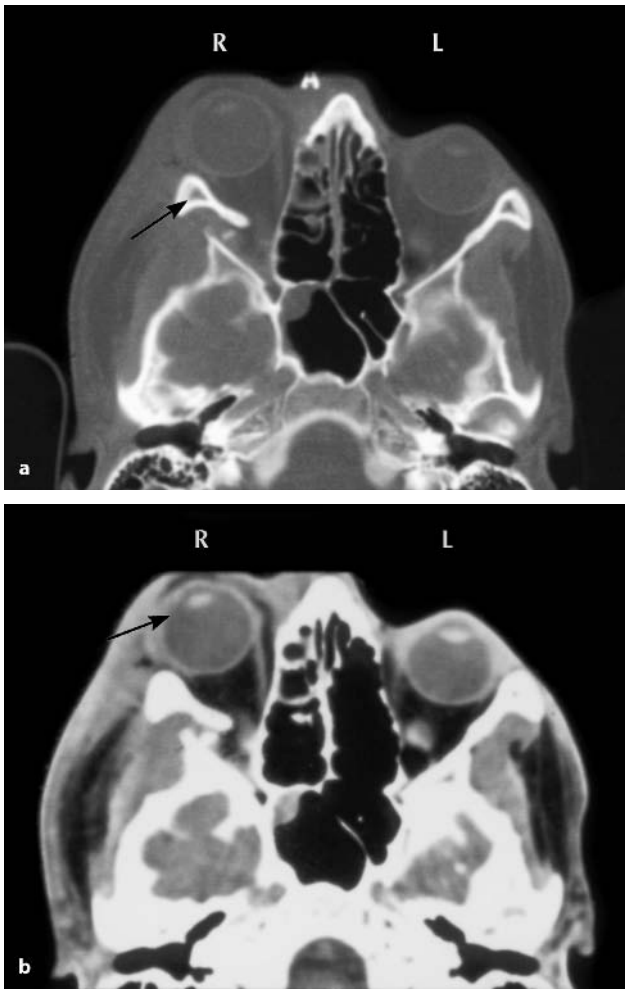


Fig. 20.2. **a** Skull/brain trauma with fracture of the lateral orbital wall on the right side: bone window showing displaced fragment of bone (*arrow*), transaxial-plane orientation. **b** Skull/brain trauma with fracture of the lateral orbital wall on the right side: soft tissue window with edema of the facial tissues and exophthalmos (*arrow*), transaxial-plane orientation

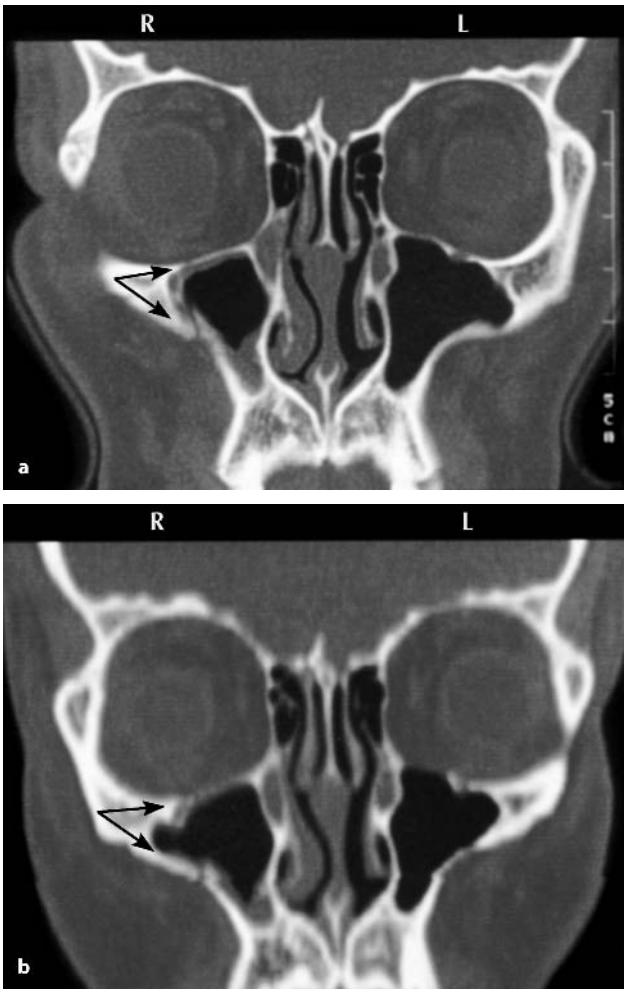


Fig. 20.3. **a** Coronal image of the orbital bones following a fracture of the orbital floor (*arrow*) and the lateral wall of the right maxillary sinus (*arrow*): initial coronal plane with sharply defined orbital floor and good demonstration of the fracture lines. **b** Coronal image of the orbital bones following a fracture of the orbital floor (*arrow*) and the lateral wall of the right maxillary sinus (*arrow*): secondary reconstruction of spiral CT data with an unsharp but still recognizable image of the fracture (*arrow*)

and minimal dental reconstructions, however, coronal images are the most revealing.

Alternatively, the data sets collected from spiral CT scans can be processed by mathematical reconstruction methods to produce calculated tomograms of whatever plane of imaging is desired (■ Fig. 20.3 b). This method is ideal for the study of critically injured patients and those with extensive dental work, since the patients can lie comfortably in a supine position. The transaxial tomographic data, collected in the planes just above the maxilla, can be used to calculate so-called secondary reconstructions (■ Fig. 20.3 b). A relative disadvantage of this approach is that significantly greater radiation doses must be used.

CT is the imaging method of choice in emergency rooms that care for patients with acute, multisystem injuries. For patients with skull/brain injuries, the presence and course of fractures in the orbit can be studied, using the windows that allow the best definition of bones' anatomy (■ Fig. 20.3). The effects of direct ocular trauma, or retrobulbar hemorrhages, are best studied when using the window settings for soft tissues. Thus, ophthalmic vein distension (■ Fig. 20.4) may be detected because of a traumatic carotid–cavernous fistula.

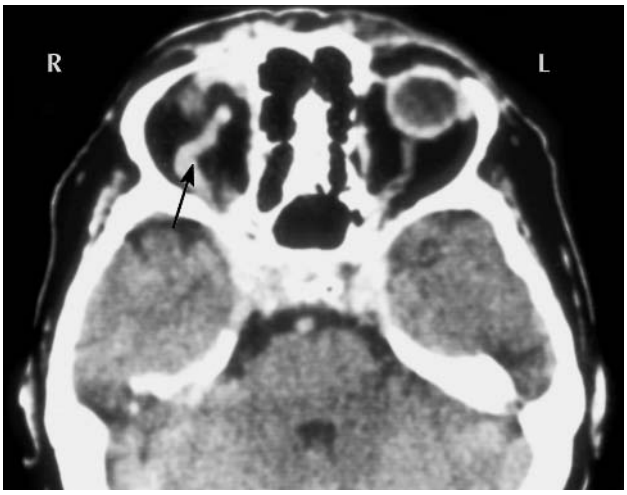
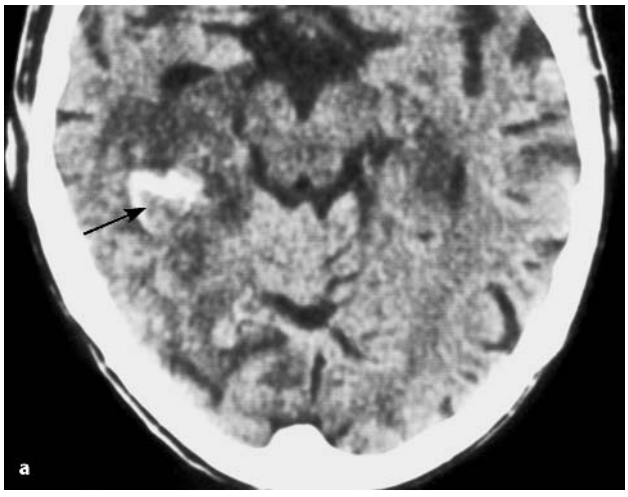


Fig. 20.4. Distention of the superior orbital vein (*arrow*) on the right side following a traumatic carotid–cavernous fistula, transaxial-plane orientation

Another indication for the use of computed tomography is the suspicion of hemorrhage or ischemia in the tissues supplied by the posterior cerebral arteries (■ Fig. 20.5). The presence of an intracranial hemorrhage is immediately demonstrable, and an area of infarction can be detected within a few hours, based on the development of a decrease in tissue radiodensity.

In the study of intraorbital and intracranial space-occupying lesions, additional information for correct classification is often obtained by CT scanning after intravenous administration of radiodense contrast material.



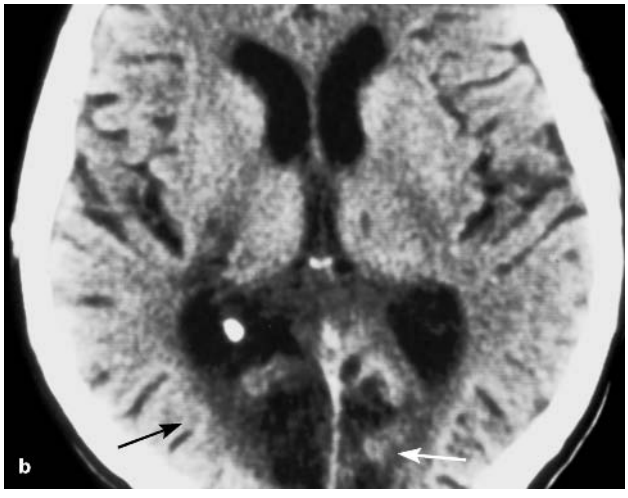


Fig. 20.5. a Ischemic disease of the posterior visual pathways: Freshly infarcted tissue (approximately 12 h) in the distribution of the right posterior cerebral artery with hemorrhage formation (*arrow*). In comparison with an older infarct, shown in **b**, there is mild swelling with erasure of the cortical sulci, transaxial-plane orientation. **b** Ischemic disease of the posterior visual pathways: Older, hypodense, and sharply demarcated insults in the visual cortex of both sides (*arrows*), transaxial-plane orientation

! Note

The following contraindications for the use of contrast materials must be observed:

- Allergy to iodinated compounds
- Hyperthyroidism
- Poor renal function
- Paraproteinemia

An important consideration is the question of total radiation exposure in patients undergoing CT studies. A cumulative radiation dose associated with 50 to 100 thin-section scans can result in radiation-induced cataract formation.

● Pearl

Another important role of CT is in the detection of tumor-related alterations in bony anatomy, as when osteolytic or hyperostotic changes have been induced (■ Fig. 20.6).

Advantages of CT as compared with MRI

The advantages of CT scanning, as compared with MRI imaging, are summarized as follows:

- Shorter examination times (2 to 5 min for CT scanning, 20 to 45 min for an MRI)
- Facilitated monitoring of rapidly changing findings
- Better assessment of bone structure
- Faster and safer detection of intracranial hemorrhages
- Lower cost

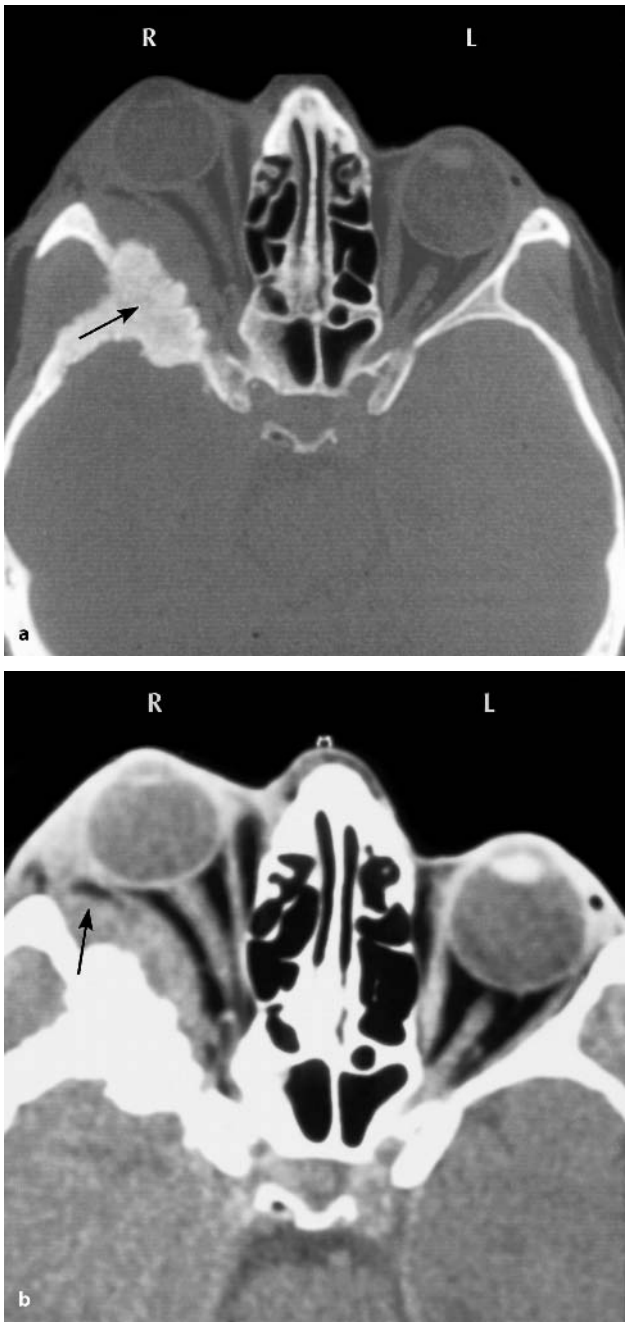


Fig. 20.6. a Sphenoid wing meningioma: tumor-induced hyperostosis (*arrow*) of the greater sphenoid wing (bone window), transaxial-plane orientation. **b** Sphenoid wing meningioma: soft tissue components of the tumor (arrow) in the lateral orbit, producing an exophthalmos (soft tissue window), transaxial-plane orientation.

Most Important Indications for CT Scanning

- Skull/brain trauma
- Stroke: differential diagnosis of hemorrhage/infarction
- Foreign-body detection
- Space-occupying lesions with bony involvement or soft tissue calcification

Due to its better soft tissue differentiation, elective MRI has increasingly replaced CT scanning of the brain and orbits. Avoidance of radiation exposure has also played a big role in these decisions.

Magnetic Resonance Imaging

Definition

Magnetic resonance imaging is a tomographic process that permits the tomographic imaging in any chosen plane within the body. This is done with the help of a strong magnetic field parallel to the long axis of the patient's body and an additional, freely variable, location-dependent magnetic field (a gradient field). In place of X-rays, the MRI uses nonionizing, radiofrequency energy.

With few exceptions, MRI today is the method of choice for the elective study of the soft tissue structures of the orbit, the optic nerve, and the intracranial portions of the visual system. In some places, the availability of MRI scanning remains somewhat limited, as compared with the availability of CT scanners. More important, though, are the following contraindications.

Contraindications to MRI

Note

Absolute contraindications (patient endangerment):

- Cardiac pacemakers
- Incorporated ferromagnetic foreign bodies/implants
- Shrapnel wounds
- Aneurysm clips of uncertain origin

Relative contraindications (no patient endangerment, but with comparatively poorer imaging quality):

- Cosmetics, such as mascara or eyeliner, with metallic content
- Nonferromagnetic metal implants, such as the metallic plates used in plastic surgical reconstructions of the face or orbit
- Cochlear implants (loss of function)
- Claustrophobia
- Inadequate patient cooperation

The minimal requirements for patient cooperation are that he/she must be able to remain immobile with no head or eye movement for the time needed to complete one measuring sequence (about 3 min).

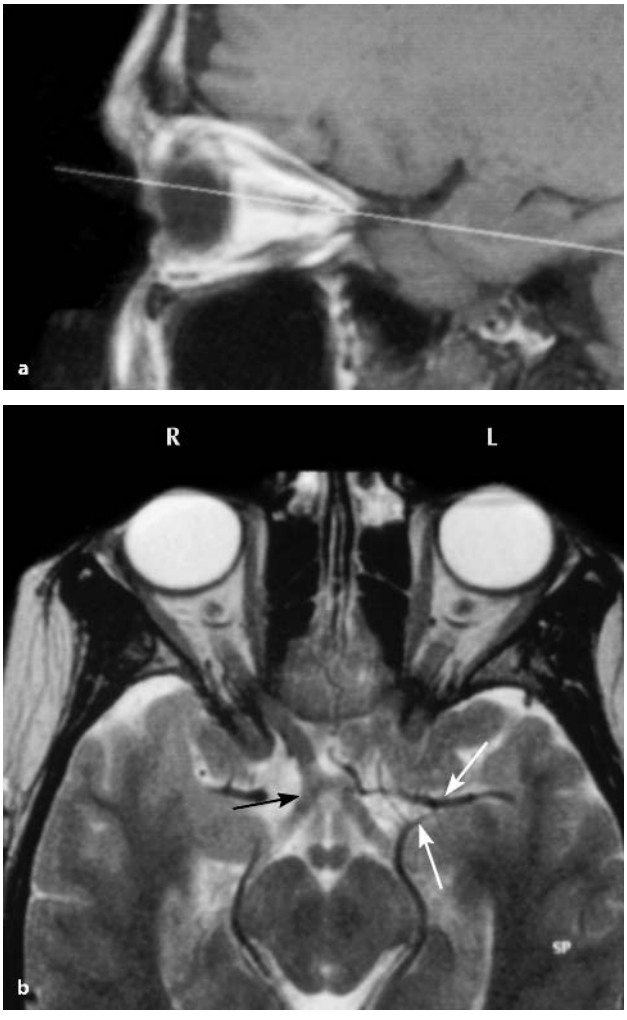


Fig. 20.7. **a** Tomographic orientation for magnetic resonance imaging (MRI) study of the orbits: parasagittal T_1-weighted (T_1w) image with a linear mark parallel to the optic nerve. **b** Normal optic chiasm with the typical "suspenders' shape" (*black arrow*), main trunk of the middle cerebral artery (*superior white arrow*). Posterior cerebral artery (*inferior white arrow*), transaxial T_2w image

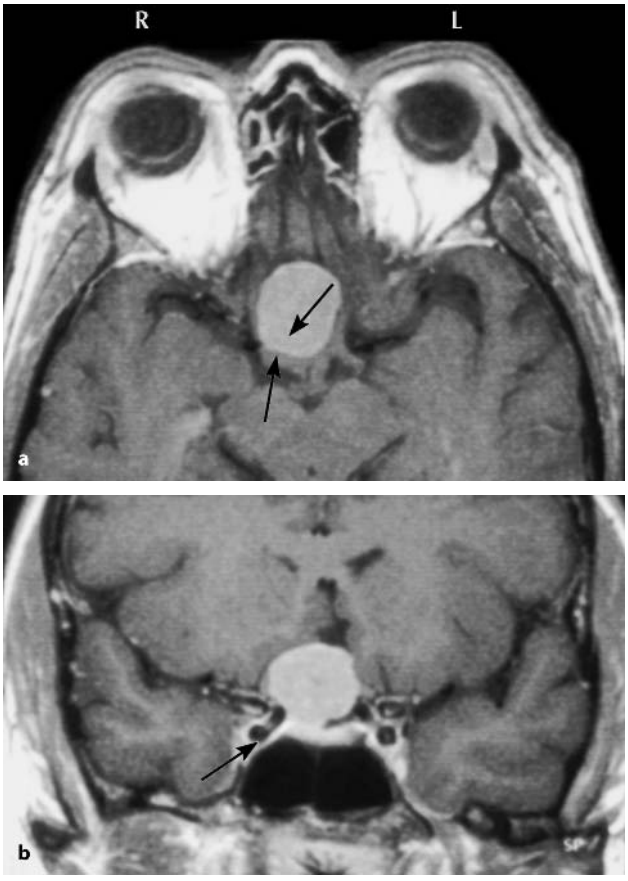
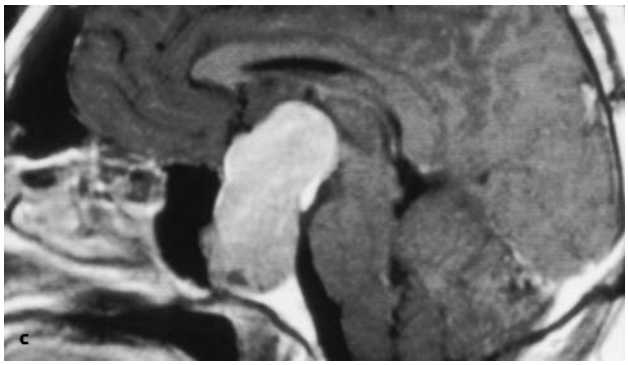


Fig. 20.8. **a** Illustration of multiplanar tomography in MR scanning in the case of a pituitary macroadenoma: T_1w contrast-enhanced study of a pituitary macroadenoma (*superior arrow*) in a transaxial orientation, showing contact between the tumor and the optic chiasm (*inferior arrow*). **b** Illustration of multiplanar tomography in MR scanning in the case of a pituitary macroadenoma: coronal tomographic plane illustrating the relationship of the mass to the distal (supraclinoid) carotid (*arrow*). *(Continuation see next page)*

Advantages of MRI

If the prerequisite conditions noted above have been met, MRI scanning offers significant advantages as compared with CT scanning. Chief among them is the improved differentiation between retrobulbar soft tissues (fat, muscle, and optic nerve), between normal components of the brain (gray and white substances) and between differing forms of pathological change (infarction, hemorrhage, inflammation, and neoplasms). Additional advantages of MRI imaging lie in the use of high-frequency radio waves with no ionizing radiation at all, which is particularly important for protecting the ocular lens. Another, perhaps more important, advantage is the freedom with which data can be acquired and displayed, to study whatever tomographic section is desired without having to move the patient (■ Fig. 20.7). Also, the contrast material used in MRI scanning, usually containing a gadolinium–DTPA complex, is better tolerated than the iodinated CT contrast dye, lowering the risk of an allergic reaction substantially. Another important advantage of MRI scanning is the ease with which the sellar region (■ Fig. 20.8), the posterior fossa, and the course of the afferent visual pathways can all be clearly delineated, without the interference of image artifact caused by the dense bony structures, as is frequently encountered during CT scanning of these spaces.



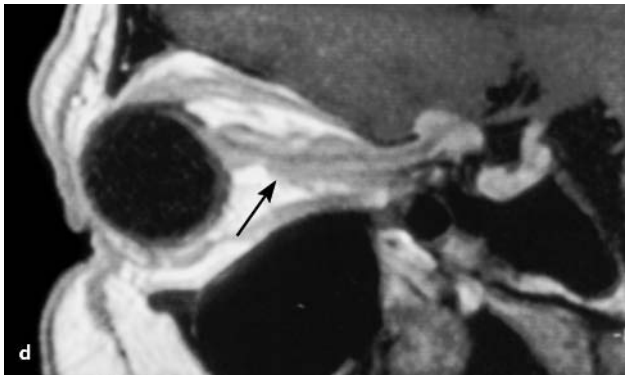
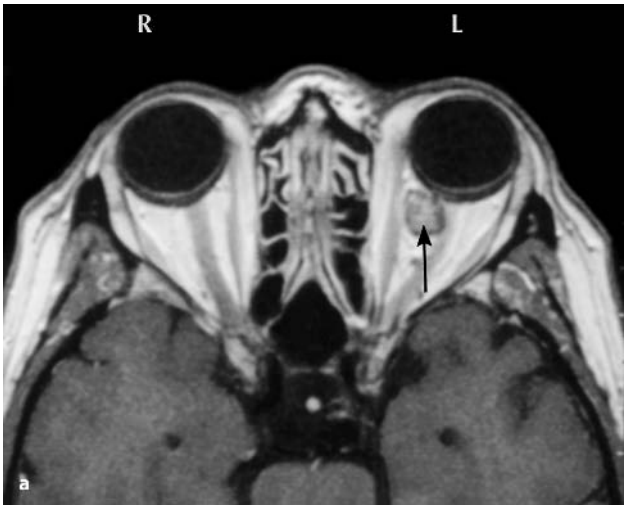


Fig. 20.8. *(Continued)* **c** Illustration of multiplanar tomography in MR scanning in the case of a pituitary macroadenoma: sagittal orientation of the tomographic plane to image the connection between the suprasellar tumor and the intrasellar remnants of the pituitary gland. **d** Illustration of multiplanar tomography in MR scanning: optic nerve sheath meningioma (*arrow*) as shown in an oblique sagittal tomographic plane (rotated about a vertical axis to an angle of about 23° away from the true sagittal plane) paralleling the course of the optic nerve

Table 20.1. Characteristic signal intensities seen on magnetic resonance imaging of the brain

	T1 weighted	T2 weighted
Cerebrospinal Fluid	Hypo-intensity*	Hyper-intensity
Fat	Hyper-intensity	Iso- or Hyper-intensity
Blood (acute hemorrhage)	Hyperintensity	Iso- or Hyper-intensity
Blood (old, hemosiderin)	–	Hypo-intensity
Gadolinium enhanced	Hyper-intensity	–

**Hypo-intensity*: dark, *Hyper-intensity*: bright



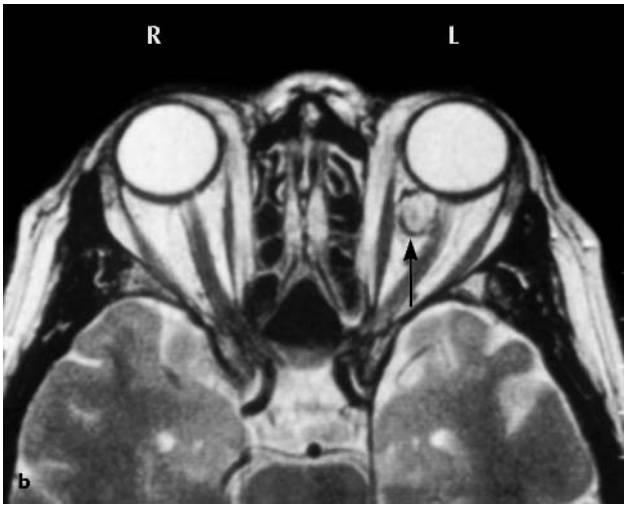


Fig. 20.9. **a** Cavernous hemangioma (*arrow*): retrobulbar tumor in the left orbit between the optic nerve and the medial rectus muscle (T_1w), transaxial tomographic plane. **b** Cavernous hemangioma: T_2w image illustrating a common feature of this type of tumor, i.e., hemosiderin deposits (*arrow*), which appear as a hypointense ring surrounding the tumor, transaxial tomographic plane

Indications for MRI

In routine diagnostic settings, a plane that is parallel to that of the optic nerves and with a thickness 2 to 3 mm provides the most useful information (■ Fig. 20.7). If additional study of intracranial contents is desired, an orientation of the plane of interest that is parallel to the line connecting the anterior and posterior commissures of the corpus callosum is ideal. A thickness of 3 to 5 mm is best. The total time for the procedure will vary from 20 to 60 min.

The most important advantage of MRI scanning lies in the fact that the signal strength in the image is not determined by measures of radiodensity, as in CT scanning, but is instead determined by tissue-specific parameters, the T_1 and T_2 relaxation times. This produces a high-resolution image with excellent tissue identification (■ Table 20.1). In the so-called T_1-weighted (T_1w) images, the cerebrospinal fluid (CSF) appears hypointense (dark), while fat, subacute hemorrhages and gadolinium-containing contrast materials appear hyperintense (bright) (■ Figs. 20.9 a and 20.10 a).

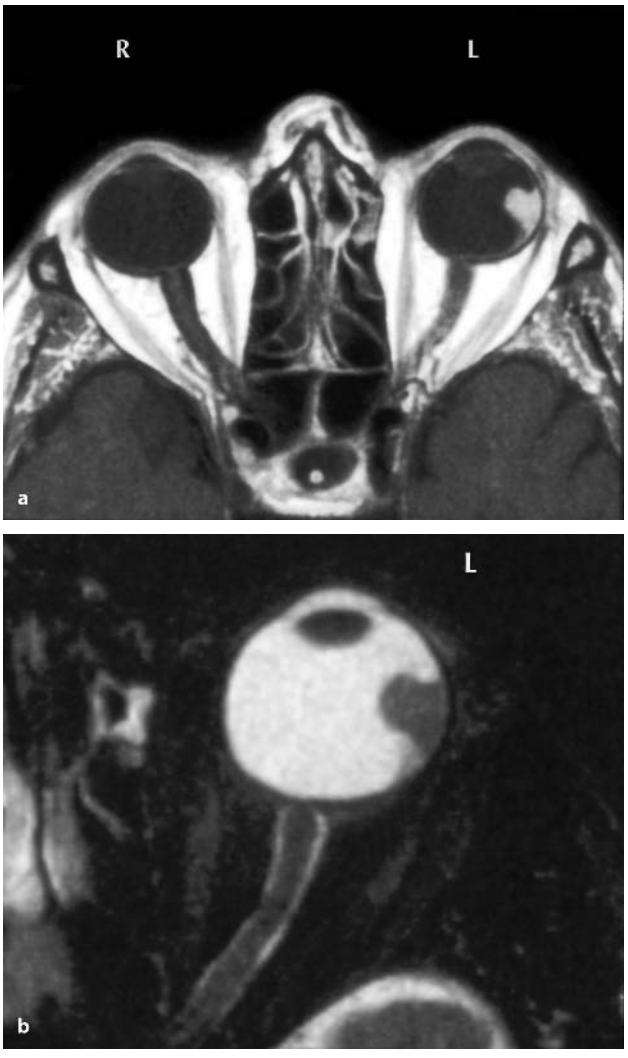


Fig. 20.10. **a** Choroidal melanoma: Contrast-enhanced study of a choroidal melanoma in the left eye, arising from the temporal fundus quadrant, near the equator of the globe, as a mushroom-shaped tumor that takes up the contrast material. Transaxial tomographic plane, T_1w, contrast-enhanced. **b** Choroidal melanoma: strong T_2w image, transaxial tomographic plane. Note the reversal of contrast: In the T_1w image (**a**) the vitreous is dark and the tumor is light, whereas in this T_2w image, the vitreous cavity is light, and the tumor appears dark

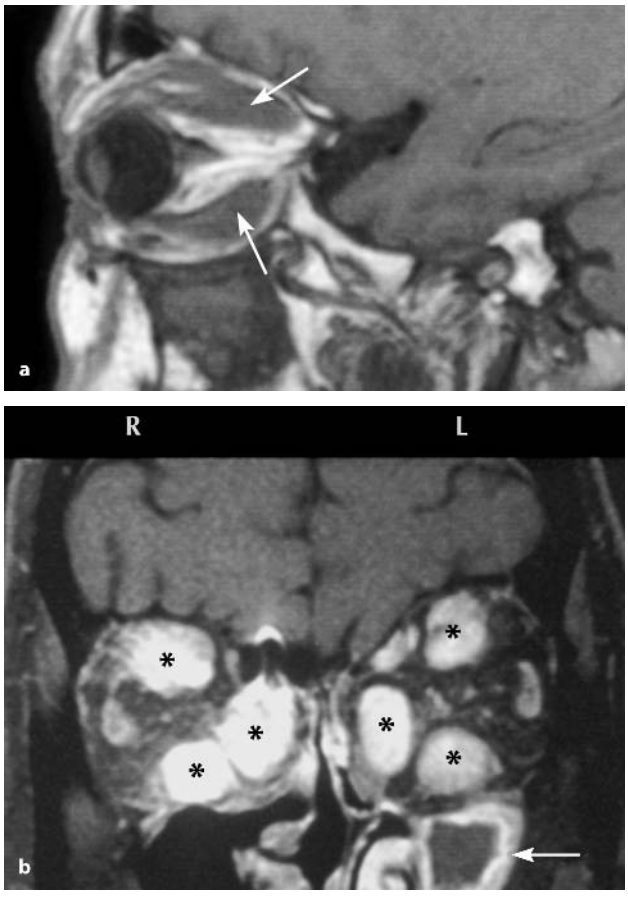


Fig. 20.11. **a** Dysthyroid ophthalmopathy: pronounced enlargement of the superior and inferior rectus muscle (*arrows*). Oblique parasagittal tomographic plane. **b** Dysthyroid ophthalmopathy: coronal T_1w, fat-sat, contrast-enhanced image of massive swelling of the medial, superior, and inferior rectus muscles in both orbits (*asterisks*). Unrelated finding of a left maxillary sinusitis (*arrow*)

In the T_2w images, the CSF and edematous tissues appear hyperintense (■ Fig. 20.9 b), but hemosiderin deposits (such as one finds in cavernomas or at the margins of old, reabsorbed hemorrhages) appear hypointense. Of particular interest for the diagnosis of orbital disease are the so-called fat-saturated ("fat-sat") images. These use a special method for the excitation of the signal given off by the retrobulbar fatty tissues, suppressing their signal strength, to allow for better definition of more subtle soft tissue features. For example, a retrobulbar lymphangiosarcoma, or changes in the extraocular muscles produced by a dysthyroid ophthalmopathy, can be more easily identified (■ Fig. 20.11 b).

Aside from the standard sequences used in T_1w and T_2w scans, more recently developed methods (such as MR angiography for studying blood vessels, and diffusion-weighted MRI for the detection of strokes) have enhanced the usefulness of MRI imaging. Diffusion-weighted scanning allows for a high level of sensitivity in the rapid detection of tissue infarction, and surrounding areas of brain ischemia, only 1 to 2 h after a stroke or stroke-like episode (■ Fig. 20.12). Other methods, such as perfusion imaging for the measurement of cerebral perfusion, and functional MRI for the determination of metabolic brain activity, are for the time being not yet generally available for routine clinical diagnosis.

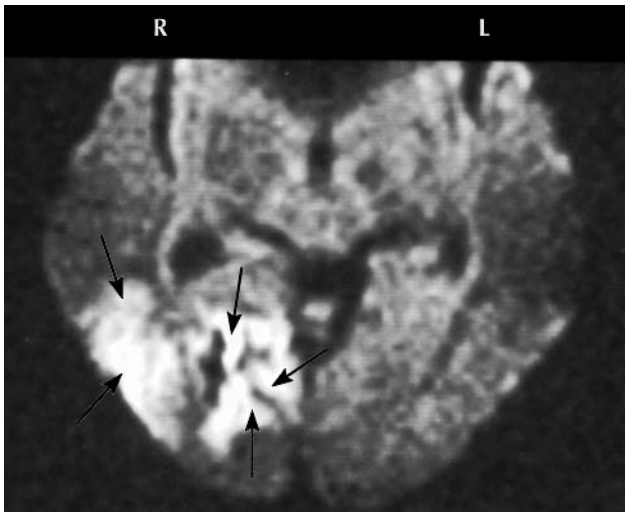


Fig. 20.12. Acute-stage occlusion of the right posterior cerebral artery (*arrows*), diffusion-weighted image. This method images the earliest change during the development of an intracranial infarction, at between 1 and 2 h after the occlusion, transaxial tomographic plane

Invasive Angiographic Diagnosis

Definition

Invasive angiography entails catheterization of the femoral artery, passage of the catheter into the vessels supplying the brain, and injection of iodinated contrast material. This approach is also used for the introduction of embolizing material (e.g., platinum coils) during invasive endovascular procedures.

The indications for invasive angiography include the diagnostic or the preinterventional study of a cerebrovascular malformation, such as an aneurysm, an arteriovenous malformation, or an arteriovenous fistula (■ Fig. 20.13). Endovascular closure by embolization is the treatment of choice for carotid–cavernous fistulas.

For a proven, acute obstruction of a central retinal artery, neuroradiologic intervention permits the direct intra-arterial injection of fibrinolytic agents, which can be successful at restoring retinal circulation and vision up to about 6 h after onset of the infarction.

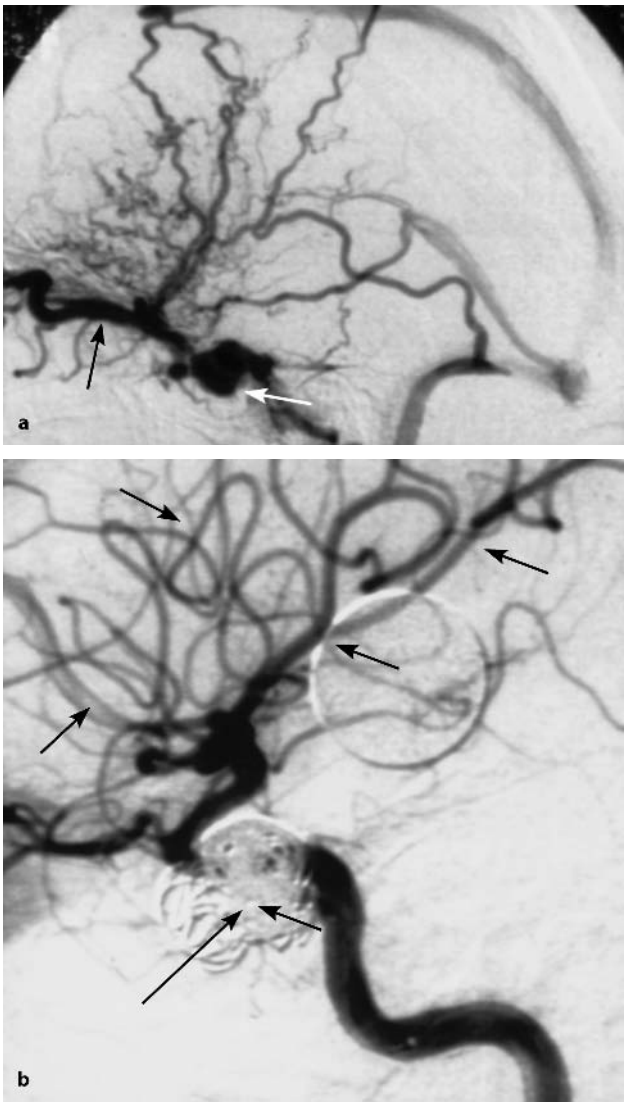


Fig. 20.13. **a** Lateral view, angiographic study of a traumatic carotid–cavernous fistula (*white arrow*). Transmission of arterial pressure into the venous tree with marked enlargement of the superior ophthalmic vein (*black arrow*). **b** Lateral view, angiographic study of a traumatic carotid–cavernous fistula (*thin arrow*). After coil embolization (*long arrow*), angiogram shows closure of the fistula with restoration of proper orthograde blood blow in the intracranial arterial vessels (*arrows in the upper half of the image*)

Important Clinical Information Needed for Neuroradiologic Investigation

Clinical features that the neuroradiologist needs for proper investigation:

- The timing of onset, the course, and the duration neurologic disease
- A summary of the findings, including visual acuity, ocular motility, and visual field defects
- Suspected location (orbit, chiasm, cerebral cortex) and side of the lesion (right or left)
- Notes regarding any relative contraindication (allergies, renal insufficiency, cardiac pacemaker, metallic implants)

Conclusion

The strategic use of modern tomographic imaging, in conjunction with the clinical findings in neuro-ophthalmic disorders, provides a reliable means for efficient diagnosis. Interventional methods expand the range of potential diagnostic and therapeutic procedures through minimally invasive endovascular treatments for vascular occlusions or malformations.

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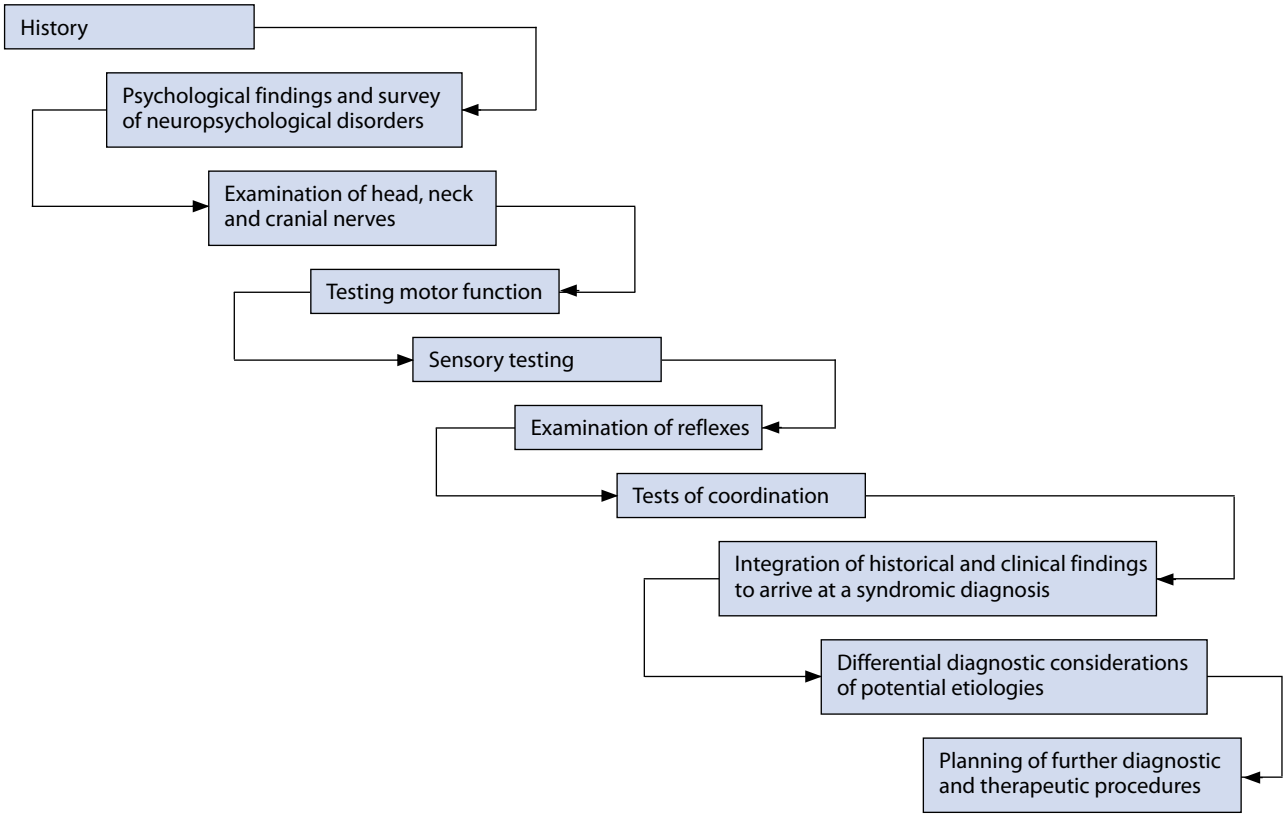
Chapter 21

Neurology

K. Gardill and H. Wiethölter

Normally, patients with visual disturbances initially seek the care of an ophthalmologist, even though the underlying cause of the problem, and more importantly its management, falls more into the field of the neurologist. The ophthalmologist is therefore heir to an important responsibility and must be on the watch for other symptoms that might accompany the visual problems. Only in this way can patients be given prompt and appropriate referral to neurological or neuroradiological consultants. Frequently, the clinician can accomplish this with only a few specific neurological tests, which can yield important information needed for the planning of further investigation and management of the problem.

As a rule, a complete neurological evaluation should be governed by a specific and well-thought sequence of tests (analogous to the sequence discussed in this chapter), to ensure that the function of all relevant systems is covered. Particularly in neurology is it generally possible to identify accurately the disease locus at fault by means of a careful clinical examination, combined with a detailed history. Given the limitations of time, an ophthalmological examination will be able to include only a few specific elements of the neurological examination, and yet with an adequate knowledge of the neuroanatomic and physiologic principles involved, should allow a close topographic localization and etiologic classification, based on a few specific symptoms and their associated findings.



History, Psychological Findings, and Neuropsychological Disorders

At the start of every neurological examination, there should be at least a minimal attempt to take a history of the patient's symptoms. This practice provides the physician with an opportunity to learn in general about the patient's psychological state, including speaking and language disorders or other neuropsychological deficits. Other individual or isolated problems may be difficult to draw out and require a more targeted form of questioning.

Psychological State

Pearl

The state of the patient's awareness of his or her identity and orientation to time and place is essential information and fundamentally important for an understanding of the problems he/she faces (■ Table 21.1).

Clues about the presence of a neurodegenerative disorder (for example, vascular encephalopathy with dementia and ocular motility disturbances, or Richardson-Steele-Olszewski syndrome with dementia and vertical gaze palsy) also help with assessing the reliability of the patient's historical accounts.

Neuropsychological Disorders

Acquired neuropsychological disorders are, as a rule, the product of pathological events affecting the cerebral hemispheres. Most commonly, these are encountered in the setting of a recent stroke. Other potential causes include hemispheric tumors, head trauma, encephalitides, and neurodegenerative diseases.

Table 21.1. Psychological data

Vigilance *(quantitative assessment of awareness)*	State of awareness	Awake, sleepy, stuporous, comatose
Orientation *(qualitative assessment of awareness)*	Temporal	"What day of the week is this? What is today's date?"
	Locational	"What city is this? What is the name of this hospital? Do you know what floor this is?"
	Situational	"Why are you in the hospital? What caused you to come to me?"
	Personal	"What is your anniversary? What are the birth dates of your children?"
Mood	*(General emotional state)*	Depressed, sullen, irritated, euphoric, anxious
Affect	*(Affective state)*	Labile affect, emotional incontinence, emotionless
Memory	*(Short-term memory)*	"What did you have for breakfast this morning?"
Recall	*(Long-term memory)*	"What is the date of your anniversary?"
Attention Ability to concentrate		Stays on the subject, does not allow digression
Intelligence/train of thought	*(Intellectual capacities)*	Slowing, diminished ability to understand, oligophrenia (congenital), dementia (acquired)
Self-awareness/critical faculties		
Drive		Lacking drive, apathetic, hyperactivity, compulsively active
Thought content		Narrow, obsessed, delusional
Illusions/hallucination		Especially visual hallucinations with organic disorders

Aphasia

Definition

Aphasias are central nervous system (CNS) disorders that cause a change in or loss of the communicative use of language. Dysarthrias are different in that they are disorders of the motor functions of speech, i.e., problems of poor verbal articulation because of loss of motor control and/or of sensory feedback within the speaking apparatus.

Pearl

Careful attention to the quality of a patient's spontaneous speech, and tests in which he/she reads aloud or repeats a spoken work or phrase will bring out otherwise unapparent problems and will mostly allow rapid classification of the type or form of the aphasia. This includes having the patient repeat words or sentences, give names to various objects, and fulfill requests to carry out simple tasks (■ Tables 21.2 and 21.3).

Apraxia

Definition

Apraxia is a central disturbance of sequences of movement and motor behaviors, despite retained motor function and coordination, mostly associated with lesions in the parietal lobes (■ Table 21.4; see also Chap. 13).

Important Signs and Symptoms (Tabulated)

Meningismus

Definition

When testing the mobility of the cervical spine, the examiner has the patient lie passively supine while raising his or her head (flexing ventrally). Painful resistance to the flexion (stiff neck) is **meningismus**.

Table 21.2. Primary symptoms of aphasia

Symptom	Definition/description	Example
Neologisms	Making up or substituting new words	"Cutter" instead of "knife"
Agrammatism	Telegram style of speaking	"Yesterday . . . eat . . . home"
Paragrammatism	Defective sentence formation with dropping off, shortening, or doubling of sentence parts	"Today I was . . . it was bread that . . . and my wife . . . no, I mean . . ."
Phonic paraphrasia	Word or syllable transposition	"Roadrail" for "railroad"
Semantic paraphrasia	Confused word use	"Fork" rather than "spoon"
Cliché speech/stereotypes	Meaningless/repetitive expressions	"But certainly nevertheless" "My goodness, my goodness"
Amnesic aphasia	Missing words are replaced with circumlocutions	"That gizmo for cutting" rather than "knife"

Table 21.3. Types of aphasia

Form	Principal signs	Locus of damage
Motor (Broca)	Elevated speaking effort Agrammatism Phonic paraphrasia Understanding of language largely retained	Left frontal lobe
Sensory (Wernicke)	Fluent, spontaneous speech with no meaning Paragrammatism Phonetic and semantic paraphrasia Neologisms Marked difficulty with understanding language	Left temporal lobe
Global	Severe disruption of all expressive and receptive functions of speech	Extensive zones of damage in the areas supplied by the left middle cerebral artery
Amnestic	Principally anomia	Posterior temporal and parietal lobes

Table 21.4. Types of apraxia

Type	Frequency, everyday relevance, affected hemisphere	Principal signs
Ideomotor	Relatively frequent, but scarcely relevant in everyday life Language-dominant hemisphere	Substitution of parts of a movement by parapraxias (= faulty components of movement, e.g., in a military salute, using a fist to the brow, rather than an open hand)
Ideational	Relatively infrequent, relevant in everyday life Language-dominant hemisphere	Cannot carry out a common sequence of actions (e.g., opening a can or preparing coffee)
Constructional	Non–language-dominant hemisphere	Loss of creative acts that depend on visual control (e.g., forming a spatial image from its individual elements – e.g., drawing an image of a house)

Meningismus is associated with meningitides and subarachnoid hemorrhages. Lasègue's sign is a similar finding. When raising the supine patient's straightened leg (flexing the hip joint), increasing pain radiating into the leg can even restrict the range of movement. This finding is also associated with compressive lesions of the lumbosacral nerve roots caused by prolapsed intervertebral discs.

Clinical Testing of Cranial Nerve Function

Isolated deficits in the function of individual cranial nerve can by caused by inflammatory (e.g., borreliosis, or idiopathic hemifacial paralysis [■ Fig. 21.1]) or by space-occupying lesions like tumors or aneurysms. In addition, abrupt mononeuropathies of the cranial nerves that innervate the extraocular muscles is frequently encountered in patients with chronic metabolic disorders, such as diabetes (■ Table 21.5).

Pearl

Clinically it is important to differentiate peripheral mononeuropathies of cranial nerves from disorders of cranial nerves associated with failures of other brainstem systems.

In addition to the central nuclei and the proximal portions of cranial nerves III through XII, which are arranged in descending order through the brainstem (mesencephalon, pons, medulla oblongata), are other important neural structures, all crowded closely together. Numerous afferents, including the dorsal columns, the spinothalamic, and the spinocerebellar pathways that connect the brain and the cerebellum with input from the spinal cord and efferent pathways (especially the pyramidal tract), all pass through this region, where many of them decussate to the contralateral side. Control of eye movements is organized in the

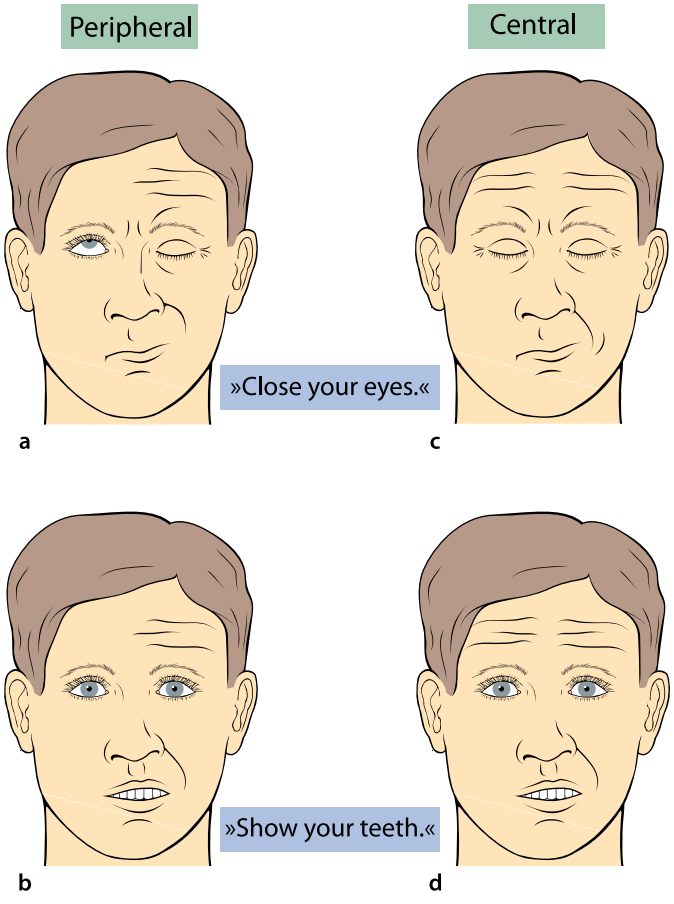


Fig. 21.1. Differential diagnosis of a facial palsy on the right side. **a**, **b** *Peripheral* facial palsy: **a** faulty lid closure with lagophthalmos and Bell's phenomenon; the patient is additionally asked to look forced upwards **b** paralysis of the perioral musculature in company with paralysis of the temporal branch of the facial nerve; **c**, **d** *central* facial palsy – **c** normal lid closure, **d** paresis of the perioral muscles and superior facial symmetry

Table 21.5. Clinical testing of the cranial nerves

Cranial nerve	Test	Pathological signs
I. Olfactory	Testing each nostril separately with eyes closed, using aromatic substances, e.g., vanilla extract or powdered coffee	Hyposmia, anosmia
II. Optic	See Chap. 8 Acuity, visual field (confrontation testing), fundus appearance (optic discs)	Reduced acuity, visual field defects, papilledema, optic disc pallor
III. Oculomotor IV. Trochlear VI. Abducens	See Chap. 10 Interpalpebral fissure, ocular motility (diplopia, oscillopsia), pupillary reactions (light/accommodation), look for nystagmus (positional and with head movement, using Frenzel's magnifying glasses)	Ocular muscle or gaze paresis, chooses eccentric gaze position, nystagmus, anisocoria
V. Trigeminal	Facial sensation, jaw muscles (open mouth against resistance, palpation of the masseters during clenching of teeth)	Peripheral ("isolated trigeminal branch") or central (onion peel dermatome) loss of sensation
VII. Facial	Facial muscles (furrow the brow, force eyes closed, turn up nose, pucker lips, blow cheeks open)	central (sparing the brow) or peripheral paresis (with Bell's phenomenon) See ■ Fig. 21.1
VIII. Acoustic	Monaural hearing tests with light rubbing of fingers together or whispering Tests of balance (nystagmus, standing, and gait tests)	Hypo-, hyper-, or anacusis
IX. Glossopharyngeal X. Vagus	Gag reflex, sensation of gums, and pharynx, swallowing Tests of palatal levators Hoarseness	Faulty swallowing, (unilateral) paralysis of palatal elevation, (pulling of the uvula towards the normal side), hoarse voice caused by paresis of the recurrent laryngeal nerve (a branch of the vagus nerve)
XI. Accessory	Head turning against resistance (sternocleidomastoids contralaterally innervated) and shoulder shrugging (superior trapezius) against resistance	
XII. Hypoglossal	Tongue protrusion	Unilateral paresis of the tongue (deviates to the healthy side) in peripheral disease and caudal brainstem disease, less so with supranuclear disease (cerebral lesions)

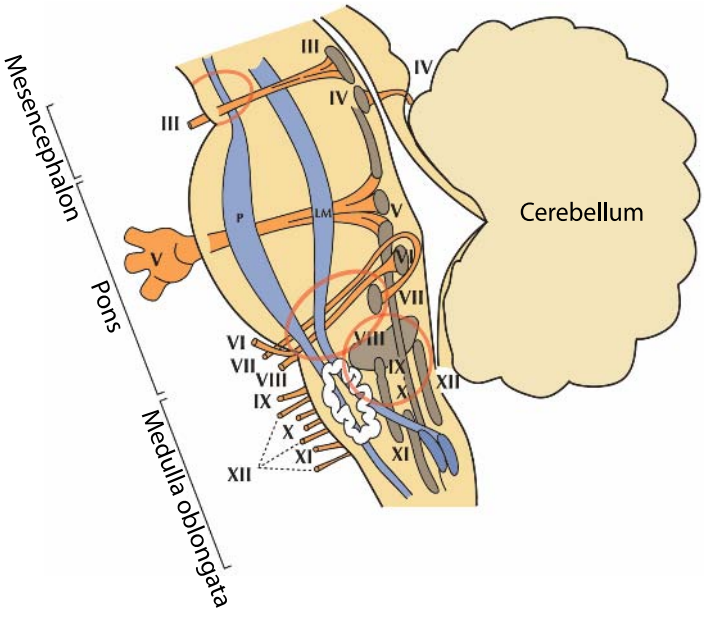


Fig. 21.2. Topographic summary of structures in the brainstem that are important for the localization of pathology: cranial nerve nuclei and cranial nerves (*Roman numerals*), the pyramidal tracts (*P*) (volitional motor function), the posterior columns (lemniscus medialis [*LM*]) and their nuclei (sensory afferents); cerebellar tracts have been left out to improve graphic depiction of other elements; the *red circled areas* are the disease locations for the most important brainstem syndromes (see Chap. 10)

midbrain and pons. In addition, important nuclei include the red nuclei in the midbrain and the olives in the medulla oblongata. Other important centers regulate consciousness, respiration, and cardiovascular circulation (■ Fig. 21.2). By analyzing the patterns of dysfunction discovered during the examination, it is possible to localize the site of a brainstem lesion with a high degree of accuracy. The most frequent causes of brainstem damage are demyelinating diseases (multiple sclerosis) in the young and ischemic vascular disease in the elderly (see Chap 10).

Nystagmus

Definition

Nystagmus is an involuntary, rhythmic oscillatory movement, usually of both eyes. In a jerk nystagmus, a slower drift in eye position is countered by sequential, intermittent saccadic movements in the opposite direction. By convention, the direction of a nystagmus is named according to the direction of the fast phase.

Physiological forms of nystagmus include positional (end gaze) nystagmus, vestibular nystagmus, and optokinetic nystagmus (OKN). Pathological types of nystagmus are most commonly the result of disorders of the brainstem or cerebellum. A simplifying rule states that nystagmus without vertigo has a central cause, whereas the type that is accompanied by vertigo is usually (though not always) caused by disease that lies outside of the CNS (■ Table 21.6; see Chap. 11).

Gaze Palsies

Definition

Gaze palsies are supranuclear disturbances of conjugate movements of both eyes.

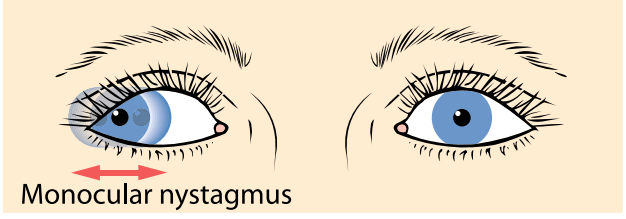
This implies that the extraocular muscles and their peripheral innervation, including the cranial nerve nuclei, are intact. The most important causes of gaze palsies are cerebral infarcts, multiple sclerosis, tumors, Wernicke's encephalopathy, and neurodegenerative disorders, such as progressive supranuclear palsy (PSP) (■ Fig. 21.3, ■ Table 21.7; see also Chap. 11).

Table 21.6. Types of nystagmus

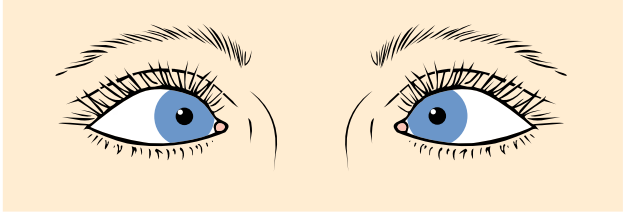
Spontaneous nystagmus	Congenital: equally fast phases (pendular)	Intensifies with fixation, no vertigo
	Peripheral: (labyrinthine disease, vestibular neuropathy)	Severe vertigo
	Central: (brainstem, cerebellum)	No vertigo
Periodic alternating nystagmus (PAN)	*Congenital or acquired, with disease of the vestibular nuclei or cerebellum. Regularly changes direction of fast phase, waxing and waning with a periodicity of about 120 s*	*No external influence*
Gaze-evoked nystagmus (present only when the direction of gaze is diverted from the primary position)	Physiologic (so-called end-gaze nystagmus)	Fatigue
	Pathologic: brainstem lesion (reticular formation), drug intoxication	Asymmetric Does not fatigue
Positional nystagmus (peripheral)	Benign paroxysmal or positional vertigo, closed head trauma	Following a rapid change in position wit a latency of several seconds, fatigues, produces vertigo
Positional nystagmus (central)	Tumors of the posterior fossa, cerebellar lesions, intoxications	Lateral position when lying, without latency and nonfatiguing, minimal or no vertigo
Downbeat or upbeat nystagmus	*By lesions in the medulla oblongata or cerebellum*	*Mostly with a dependent head position*
Gaze paretic nystagmus	Seen with partial (and even not visible) gaze palsy	
Dissociated (disjunctive) nystagmus	*Nystagmus predominantly in one eye in association with brainstem disease*	*Most common form is that seen in internuclear ophthalmoplegia*
Optokinetic nystagmus (OKN)	Physiologic, e.g., gazing out at passing landscape from a moving vehicle	Can be tested with an optokinetic drum or tape, pathological asymmetry found with lesions of the temporoparietooccipital region (Area 19) see ■ Fig. 13.1

Table 21.7. Gaze palsies

Form	Signs and symptoms	Site of damage	
Horizontal gaze palsy	Volitional gaze movement to the left or right is not possible	• Ocular motility centers of the frontal cortex (Brodmann area 8) • Corticonuclear pathways • Pons (paramedian pontine reticular formation or PPRF)	There is usually a transient period of conjugate deviation to the ipsilateral side (with cortical disease) or the contralateral side (with brainstem lesions)
Vertical gaze palsy	Volitional gaze movement up or down is not possible	• Midbrain	Note that restricted upgaze in the elderly is an aging phenomenon and is not usually pathological
Internuclear ophthalmoplegia (INO)	Paralysis of adduction of one eye with retained convergence (indicating a functional medial rectus muscle) and a simultaneous monocular abducting nystagmus of the contralateral eye (see ■ Fig. 21.3)	• Posterior medial longitudinal fasciculus (MLF) connecting the cranial nerve nuclei of the third and sixth cranial nerves (pontomesencephalic)	Frequently subtotal and evident as a visible slowing of saccadic velocity of the adducting eye Frequently bilateral
One-and-a-half syndrome	A combination of an INO and a gaze paresis to the ipsilateral side (see Chap. 11)	• Pons	



a Right gaze



b Convergence

Fig. 21.3. Internuclear ophthalmoplegia (INO), left side. **a** Paresis of adduction of the left and monocular nystagmus of the right eye on gaze to the right side. **b** Normal adduction during accommodative convergence, proving that the medial rectus itself is unaffected

Dysarthria

Definition

Dysarthria is a disturbance of the motor control of speech, resulting in poor articulation.

In contradistinction to aphasia, which is categorized as a neuropsychological deficit (see above), dysarthria is a purely motor disturbance of the mechanics of speech. The understanding of language is unaffected, so communication is less severely affected by dysarthrias than it is by aphasias (■ Table 21.8).

Clinical Testing of Motor Function

Tests of arm and leg positional stability provide a way of quickly detecting the presence of a motor deficit, as for example, following a suspected stroke (■ Fig. 21.4). Relatively subtle motor disturbances can be detected by this sort of testing, although it does not contribute much to a differential diagnosis of the source of the problem. In addition, peripheral pareses of individual nerves or nerve roots can sometimes be missed.

Table 21.8. Dysarthrias

Form	Principal signs and symptoms	Locus of disease
Cortical	Poor articulation of consonants	Cerebral (e.g., following ischemic stroke)
Pseudobulbar	Poor consonants, monotone intonation, and slowing of speech	The cerebral cortex and the pathways to the cranial nerves (supranuclear, frequently associated with small vessel disease)
Bulbar	Muffled speech ("a lump in my throat") or nasal intonation of speech	Brainstem (e.g., ischemic disease), peripheral nerves (e.g., in amyotrophic lateral sclerosis (ALS), motor end plates (e.g., myasthenia), musculature (e.g., muscular dystrophy)
Extrapyramidal	Monotone intonation, soft voice	Basal ganglia or their connections (e.g., Parkinson's disease)
Cerebellar	Fragmented, irregular, blurting speech Inappropriate stressing of words, a raw and deep voice	Cerebellum (particularly with multiple sclerosis)

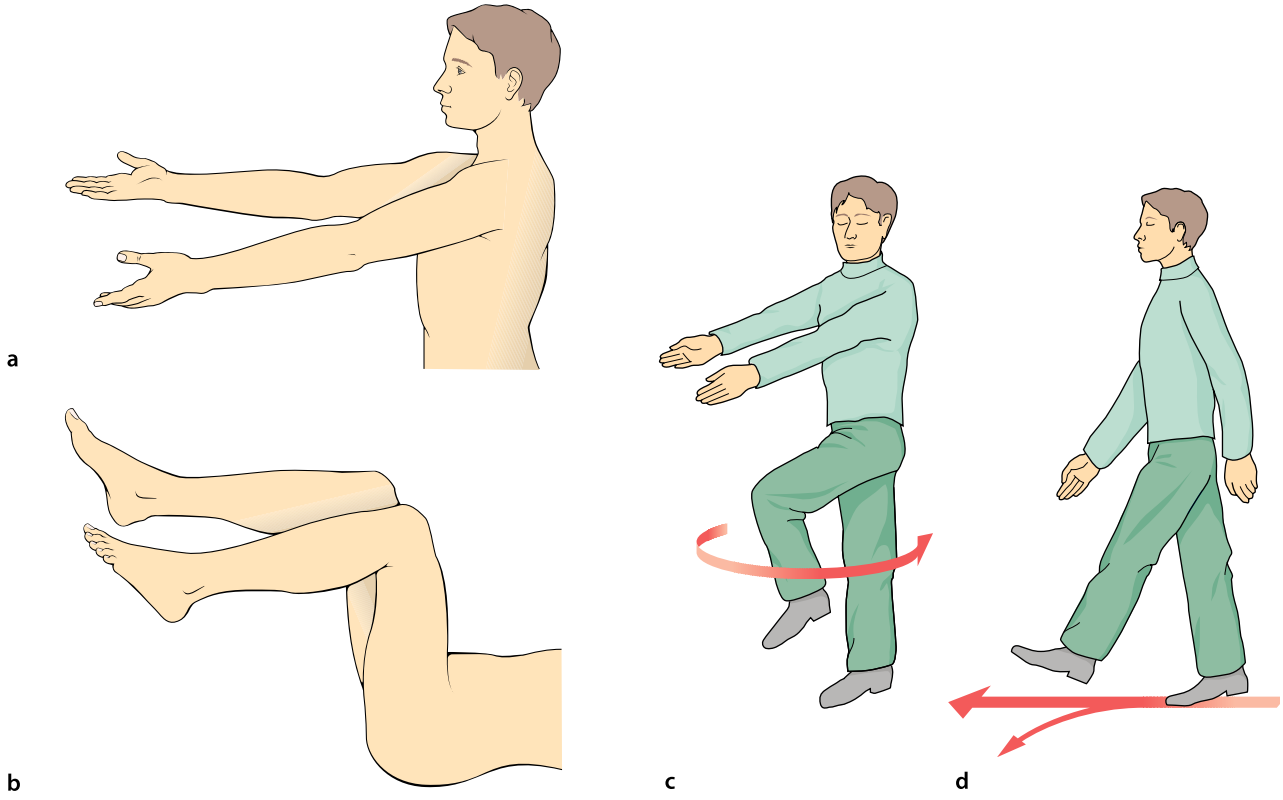


Fig. 21.4. **a** Downward drift and pronation of the left arm during an attempt to hold the limb in a steady and extended position. **b** Sinking of the left leg during an attempt to hold it in a steadily raised position. **c** Unterberger's test: The patient stands and "walks in place" with eyes closed. A fresh vestibular lesion is indicated when a body turn of more than 40° appears within 1–2 minutes (the patient turns in the direction opposite to that of the nystagmus). **d** Walking with closed eyes in a straight line results in a deviation to one side or the other: the side opposite to that of the nystagmus.

Pearl

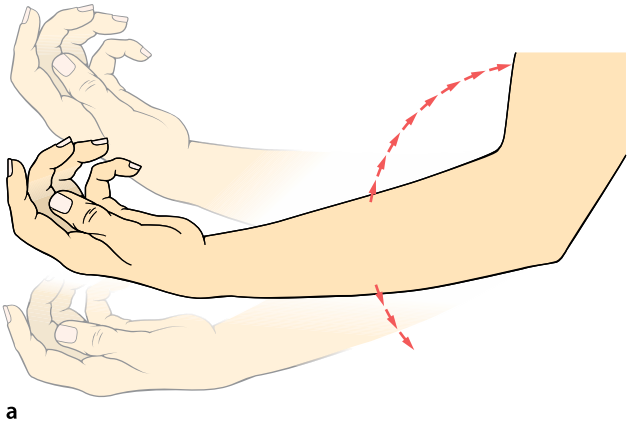
For a complete analysis of motor deficits, the positional stability tests should be augmented with attention to the signs of atrophy, the strengths of specific muscle groups, and the muscular tone of the neck and the extremities (■ Fig. 21.5, ■ Table 21.9).

Diagnostic conclusions about the location of damage can be drawn from the topical distribution of pareses. Therefore, for example, a hemiparesis immediately alerts the examiner to the presence of a central disorder (■ Fig. 21.6). Additional clues for distinguishing between central and peripheral pareses are listed in ■ Table 21.10.

Video 21.1

Table 21.9. Examination of motor function

Inspection		
Signs of atrophy	Particularly in peripheral neuropathies and myopathies	
Movement unrest	Myokymias (quivering movements spread across broad muscle groups)	Frequently normal Often facial in patients with multiple sclerosis
	Fasciculations (brief contractions of individual muscle portions [motor units])	Sometimes normal, pronounced in ALS, spinal muscle atrophy, and poliomyelitis (including postpolio syndrome)
	Fibrillations (contractions of individual muscle fibers, very small, directly visible only in the tongue)	In ALS
Muscle tone	Passive movement of limbs during complete relaxation of muscles, especially those of the neck, elbows, wrists and knees (see ■ Fig. 21.5)	
Diminished	Sleep/hypotony	Acute central paresis Peripheral paresis Cerebellar disease
Elevated	Spasticity Elastic resistance to movement „clasped knife phenomenon“	Most central pareses
	Rigidity Constant resistance to movement, often with the “cogwheeling phenomenon”	Extrapyramidal motor disease
Muscular strength		
Stationary holding of arm position/ leg position	Detects mild or “latent” pareses when weakening is not readily apparent	See ■ Fig. 21.4
Severity of pareses	Degree of weakness: 0/5 = totally paralyzed to 5/5 = completely normal strength	Test the strength of the most important joint movements: The patient is asked to contract a certain muscle or muscle group with maximal force, while the examiner resists the movement
Diadochokinesia (ability to perform rapidly alternating movements)	A test of fine motor control; also detects mild pareses	Rapid alternating pronation and supination of the wrists, typing, replacing light bulbs
Hyperkinesias		
	Tremor, chorea, athetosis, ballismus, dystonia, tics, myoclonus	Largely CNS disease, extrapyramidal disease



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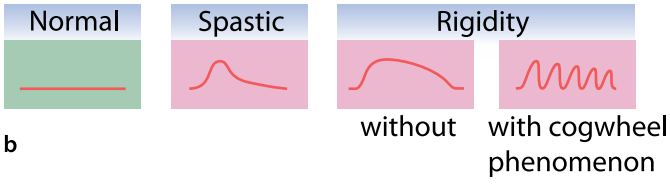

b

Fig. 21.5 a Testing of the muscle tone around the elbow joint by passive manipulation during maximal relaxation of the muscles. **b** Diagram of important pathological findings the pocketknife phenomenon (fading of resistance when under steady pressure), and cogwheeling (joint rigidity with repeated, brief, and uniform increases in tonus over the entire range of motion of the joint) in case of muscle rigidity in Parkinson's disease

Table 21.10. The differential diagnosis of central and peripheral pareses

	Central pareses	Peripheral pareses
Fine motor control	Diminished	Largely unaffected
Muscular atrophies	None	Manifest
Tonus	Elevated spastically	Weakness
Deep tendon reflexes	Amplified (and possibly associated with clonus)	Weakened or extinguished
Pathological reflexes	Manifest	None
Coarse movements	Manifest	None

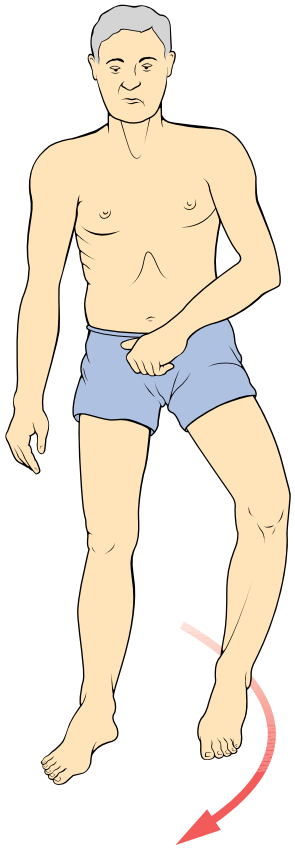

Fig. 21.6. Wernicke-Mann gait with hemiparesis of the left side following an infarct in the region supplied by the right middle cerebral artery: flexed, pronated, and adducted position of the left arm, extended left leg with plantar flexion and a partially supinated foot, forcing the patient's movement of the leg into an arc that swings out to the side

Pearl

Pareses of an extremity analyzed by strength testing of individual muscle groups usually allows for a rapid classification of the locus of disease to nerve root, plexus, or peripheral nerve. Additional clues are provided by accompanying disturbances of sensory function and testing of reflexes.

Clinical Testing of Sensory Function

When testing sensory function, the examiner has to rely on the attention and cooperation of the patient. A thorough testing of the most important sensory modes can be time-consuming (■ Tables 21.11 and 21.12).

Pearl

During a quick survey, or when examining patients that are only poorly cooperative, testing of pain sensation (with a needle or a toothpick) provides the most useful information.

From the topography and the quality of sensory disturbances, one can frequently reach an accurate conclusion as to the localization and etiology of the neural pathology. Typical examples are illustrated in ■ Fig. 21.7.

Clinical Testing of Reflexes

In general a minimal neurologic examination should include the most important arm and leg reflexes (■ Tables 21.13, 21.14, and 21.15), as well as testing of the presence of one of the Babinski signs. Deep tendon reflexes should be tested in positions that allow maximal relaxation of the involved muscle groups. This is most likely to be the case with the patient in the recumbent position. If muscular tension is fully excluded, and the patient still has absent or very weak deep tendon reflexes, facilitation maneuvers are often helpful, such as clenching the teeth during tests of arm reflexes and grasping both hands together while exerting maximal effort at pulling them apart (Jendrassik's maneuver), during the testing of leg reflexes.

Table 21.11. Esthesiometry (estimates of sensory function)

	Sensation	Method of examination	Pathological signs
External sensation	Touch	Stroke with fingertip, or even better use a small sable brush or wad of cotton	Hypesthesia Anesthesia Hyperesthesia
	Pain	Toothpick Disposable safety pin	Hypalgesia Analgesic Hyperalgesia
	Temperature	Test tubes filled with cold and warm (not hot!) water	Thermhypesthesia Thermanesthesia
Deep sensation	Position	With eyes closed, move limbs to the positions indicated by examiner's manipulation of the corresponding contralateral limbs	
	Motion	With eyes closed detect the direction of passive movements of distal interphalangeal joints	
	Vibration	Apply tuning fork to surfaces with palpable subcutaneous bone (0–8/8)	Pallhypesthesia Pallanesthesia
Combined	Stereognosis	With eyes closed identify small objects placed in the hands	Astereognosis

Table 21.12. Additional pathologic signs/symptoms of sensory systems

Dysesthesia	Sensory perception is unpleasantly altered, e.g., touch is felt as pain
Paresthesia	Unpleasant sensations (itching, burning, formication) that are spontaneous, or elicited by gentle surface stimuli
Hyperpathia	Sensations are amplified and are felt as unpleasant, e.g., hyperalgesia
Dissociated sensory loss	Isolated sensory modalities lost within a body part, with other sensory modalities retained

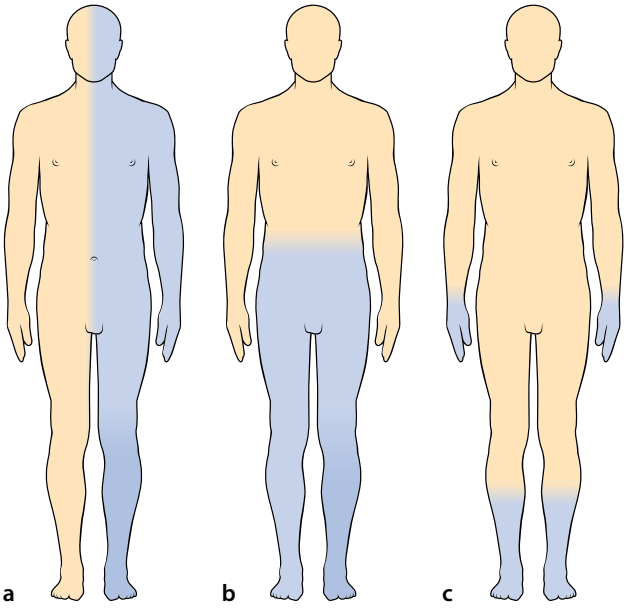

Fig. 21.7. Common patterns of sensory loss. **a** Unilateral loss of sensation with lesions of the contralateral cerebral hemisphere. **b** Loss of sensory perception in both legs with transverse damage to the spinal chord. **c** Glove-and-stocking pattern of sensory loss associated with a polyneuropathy

Deep tendon reflexes are variably elicitable under normal circumstances among patients in general. They can be quite weak in some patients, and lively in others. In order to identify correctly pathological weakening, care should be taken to compare one side to the other, to compare leg reflexes with those of the arm, or the arm and leg reflexes to those of the masseter. Pathological weakening of these reflexes should be diagnosed only when a clear and definite departure from normal can be detected.

Clinical Testing of Coordination – Ataxia

Definition

Disturbances of coordination, i.e., of smoothly cooperative alternation of agonists and antagonists during the course of complex movements like walking, are in general referred to as **ataxia**.

Table 21.13. Types of reflexes

Type	Neurophysiology	Example	Peripheral disease	Central disease
Deep tendon reflexes (DTRs)	Stimulus site and responding body part are in the same muscle, monosynaptic reflex arc, no adaptation	Achilles reflex	Diminished or extinguished	Amplified
Superficial reflexes	Receptors mostly in the skin, responses in neighboring musculature, polysynaptic reflex arc spread over several adjacent spinal dermatomes, adaptation is typical	Physiologic: abdominal reflexes	Weakened or extinguished (measured only by comparisons of symmetrical sites)	Weakened or extinguished (measured only by comparisons of symmetrical sites)
		Pathologic: Babinski reflex	Not elicitable	Elicitable

Table 21.14. Important reflexes of cranial nerve function

	Neurophysiology	Examination method	Significance
Masseter reflex	Monosynaptic muscular reflex Receptor and effector functions served by trigeminal nerve Synapse located in pons	Examiner places index finger transversely across slack-hanging jaw, striking the finger with a reflex hammer The response is a brief elevation of the mandible	Very brisk or amplified with supranuclear lesions affecting the corticopontine pathways (first motor neuron)
Corneal reflex	Oligosynaptic reflex, afferent path in the first (ophthalmic) division of the trigeminal nerve, efferent path via the facial nerve, synapses located in pontomedullary brainstem	Touch cornea with a cotton wisp that is not visible to the patient, response is a blink produced by a contraction of the orbicularis oculi	Attenuation caused specifically by lesions of the trigeminal or facial nerve or their central synaptic connection

Table 21.15. The most important intrinsic and extrinsic muscle reflexes

Reflex	Common abbreviation	Segment/peripheral nerve	Examination technique
Biceps tendon reflex	BTR	C6/musculocutaneous	Striking the index finger of the examiner, as it is held against the biceps tendon
Brachioradialis reflex (radioperiosteal reflex)	RPR	C6/radial	Striking the distal third of the radius
Triceps tendon reflex	TTR	C7/radial	Striking the tendon just above the olecranon
Trömner's reflex		C8/median > ulnar	Fingers 2–5 of the examiner quickly tap the tips of the flexed fingers 2–5 of the patient with his or her hand held in a relaxed, dorsiflexed position
Adductor reflex	ADR	L3–4/obturator	Striking the medial aspect of the knee joint
Patellar tendon reflex	PTR	L4/femoral	Striking the patellar tendon
Achilles tendon reflex	ATR	S1/tibial	Striking the Achilles tendon
Abdominal reflex	AR	Th7–12	Examiner uses a small wooden dowel or similar blunt object to quickly stroke the abdominal surface (from the lateral aspect towards the midline) in the superior, middle, and inferior thirds

Table 21.16. Tests of coordination

Test	Method	Pathological signs
Diadochokinesis	Screwing in a light bulb Rapid alternating pronation/supination at the wrist Playing piano/typing	Dysdiadochokinesis is found in pareses, lesions of the basal ganglia or cerebellum, and disturbances of deep sensation.
Finger-to-nose test Finger-to-finger test Heel-to-knee test	Look for: Smooth accuracy of movement Fluency of the movement Is there an intention tremor?	Dysmetria (see disturbances of cerebellar function)
Rebound movement	The patient (with eyes closed) presses with an extended arm with maximal upward force against the examiner's resistance. Cessation of resistance results in a quick response that prevents uncontrolled elevation of the patient's arm.	Abnormal rebound movement is found in patients with cerebellar dysfunction: The arm rises uncontrollably.
Bárány's pointing test	The patient lowers an extended arm, first with eyes open, then with eyes closed, until his/her index finger is aligned with that of the examiner's.	Poorly controlled movement with cerebellar or vestibular disease. Effect magnified with eyes closed, removing visual feedback control
Standing test, including Romberg	The patient stands with lowered, then with extended arms, and the test is repeated with eyes closed.	Unsteadiness (standing ataxia) with cerebellar disease Increasing with eyes closed, when there is also loss of sensory afferent control (loss of proprioception and touch sensations).
Unterberger step test ■ Fig. 21.4 c	Walk in place with arms extended and eyes closed (must be repeated several times)	Turning around the truncal axis (toward the diseased side) in patients with cerebellar or vestibular disease
Gait test ■ Fig. 21.4 d	Walking movements under various conditions of increasing difficulty (eyes closed, simulated tightrope walking, hopping on one leg)	Gait ataxia (e.g., in cerebellar disease) Small steps with faulty or absent associated movements like arm swing in patients with Parkinson's disease Wernicke-Mann gait after middle cerebral artery infarct

Table 21.17. Summary of signs and symptoms of cerebellar disease

Disorder	Clinical test or finding
Cerebellar dysarthria	See above, see ■ Table 21.8
Resting and gaze-evoked nystagmus	See above, see ■ Table 21.6
Intention tremor	In the finger-to-nose test, the tremor appears at the end of the movement just in front of the nose
Truncal, postural, and gait ataxia	Standing and walking test (■ Table 21.16)
Dysmetria	Poor judgment of targeted movements (pointing test; ■ Table 21.16)
Abnormal rebound movements	Hypermetric movements (■ Table 21.16)
Asynergy – dysdiadochokinesis	Faulty coordination of muscles for specific movements
Muscle flaccidity	See above (motor function)

Normal coordination depends on the simultaneous participation in the function of multiple neuronal systems (■ Table 21.16). Among these are the cerebral hemispheres, the cerebellum, the spinal, extrapyramidal, and vestibular systems, as well as the afferents and efferents of the peripheral nervous system.

Disturbances of Cerebellar Function

Cerebellar disorders are detected most sensitively with tests of coordination (■ Table 21.17). Important clinical signs of cerebellar dysfunction have been described in patients with multiple sclerosis with the so-called Charcot's triad: intention tremor, nystagmus, and scanning speech.

Conclusion

When visual changes are thought to be caused by a disease process affecting the nervous system, the ophthalmologist should, as a "non-neurologist," be able to elicit important clinical signs that will help to clarify the neurological diagnosis. This should help reduce the number of suspected disorders in the differential diagnosis, and by eliminating some possibilities, will facilitate the planning of further diagnostic procedures. This is especially important when assessing the level of urgency associated with the findings, and to participate in the strategic planning of the patient's further care.

Further Reading

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Chapter 22

Neurosurgery of the Visual Pathway

A. Gharabaghi, J. Honegger, and M. Tatagiba

The visual pathways take an extraordinary and extensive intraorbital and intracranial course from the globe to the visual cortex within the occipital lobes. Hence, a large number of orbital and intracranial pathologies interfere with the optic pathways. The diagnosis and treatment of these pathologies demands an interdisciplinary team with ophthalmologists, neuroradiologists, neurosurgeons, and radiation therapists. The management algorithm takes into consideration presenting signs and symptoms, as well as ophthalmologic and imaging findings. It requires a multimodal treatment protocol depending on the biological nature and location of the pathology.

Modern neurosurgery applies a vast range of operative approaches and microsurgical techniques to remove intra- and extra-axial lesions of the optic pathways. The neurosurgical management is enhanced by recent advances of intraoperative image guidance and electrophysiological monitoring to face the challenge of preserving function.

Tumors Compromising the Visual Pathway

When visual loss is associated with a mass lesion, the physician in charge has to consider a large variety of aspects such as the biological nature and the location of the lesion. Is the tumor extra-axial, i.e., originating in the vicinity of the optic system and compressing it, or is it intra-axial, i.e., arising from the visual pathway itself? Is the lesion slow or fast growing? Does it threaten the patient's life? What is the probable time course of further deficits to be expected? Can the lesion be removed completely, or does the surgery have to be limited to decompression of the visual pathways? Furthermore, the surgical accessibility and appropriate operative approach has to be considered in terms of adequate tumor exposure and minimal invasiveness with satisfying cosmetic results at the same time. Which additional imaging and electrophysiological information is available to increase the safety of the intervention?

The intention of the following chapter is to address these questions for the most frequent tumors of the orbita, anterior skull base, sellar/parasellar region, and intraparenchymal hemispheres that compromise visual function, and to introduce the required neurosurgical techniques including intra- and extracranial approaches to treat these lesions.

Intraorbital Lesions

Definition

Intraorbital tumors include optic nerve sheath meningeomas, optic nerve gliomas, cavernous hemangiomas, peripheral nerve tumors, dermoid and epidermoid cysts, osteomas, fibrous dysplasia, hemangiopericytoma, metastatic lesions, and less frequent pathologies.

Note

Orbital tumors that are located lateral to the nerve may be resected via a lateral orbitotomy. Lesions superior to the optic nerve are removed using an orbitofrontal craniotomy. When the tumor is located below the nerve or medially, a transethmoidal or transmaxillary approach or a transconjunctival approach can be chosen.

Optic nerve sheath meningeomas (■ Fig. 22.1) may be treated with a variety of modalities, depending on the current visual status of the patient. If vision is lost completely, the tumor can be removed totally. When useful visual function is present, fractionated stereotactic radiotherapy is the method of choice (see Chap. 23). From the neurosurgical point of view a histological confirmation should precede this therapeutic option.

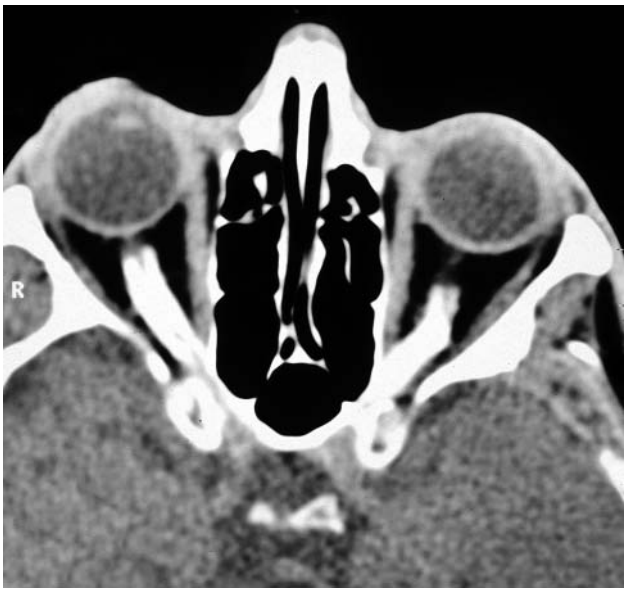


Fig. 22.1. Bilateral optic nerve sheath meningiomas. The CT images show an extensive calcification of the lesions

Pearl

Optic nerve gliomas are often associated with neurofibromatosis type 1 and occur typically in the first decade of life (■ Fig. 22.2). Surgery has to be considered when loss of vision or radiological progression occur. In these cases, the nerve is resected with the tumor via a frontolateral approach to prevent chiasmatic involvement (■ Fig. 22.3).

Cavernous hemangiomas are the most common benign primary orbital tumor of the adult and can be removed completely. The surgical approach depends on the location of the lesion in relation to the optic nerve. Most often fronto-orbital craniotomies are performed.

In special cases of endocrine orbitopathy with deteriorating visual function, orbital decompression may be helpful (■ Fig. 22.4).

After trauma, decompression of the optic nerve is indicated in cases of deteriorating visual function or in association with the treatment of cerebral spinal fluid fistula and/or intraorbital hematoma (■ Fig. 22.5).

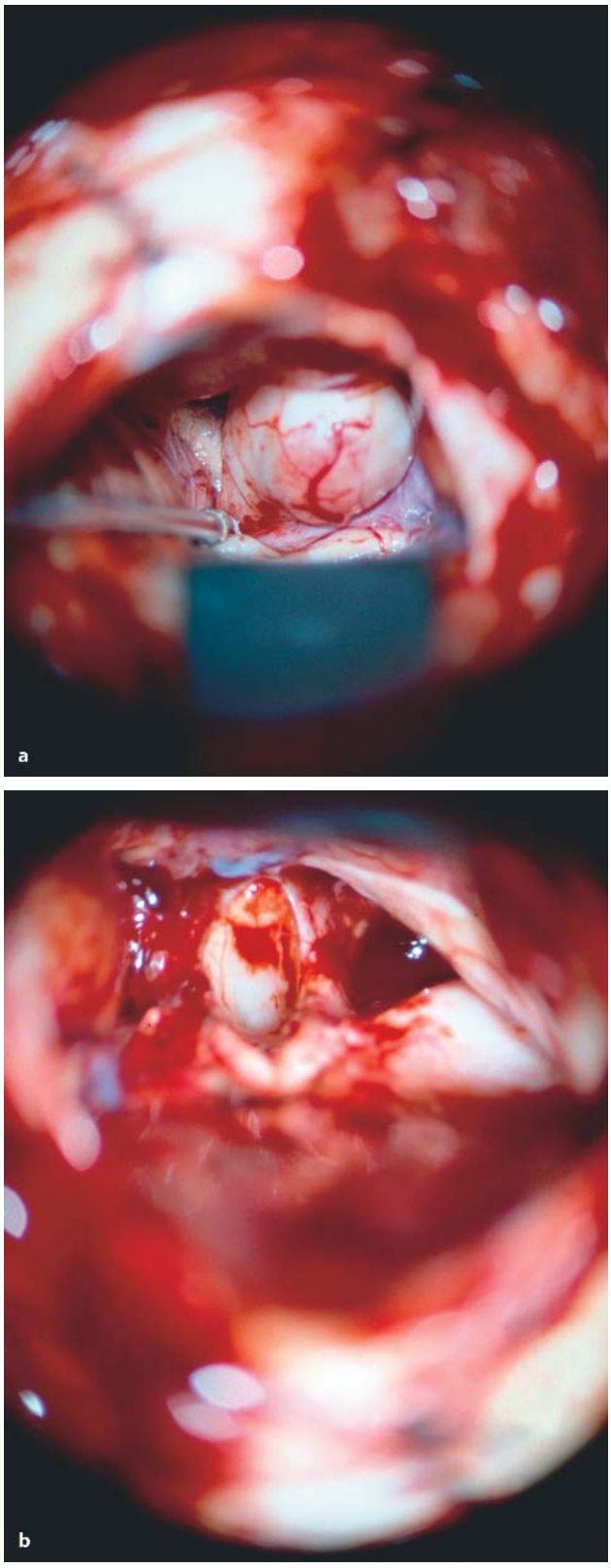
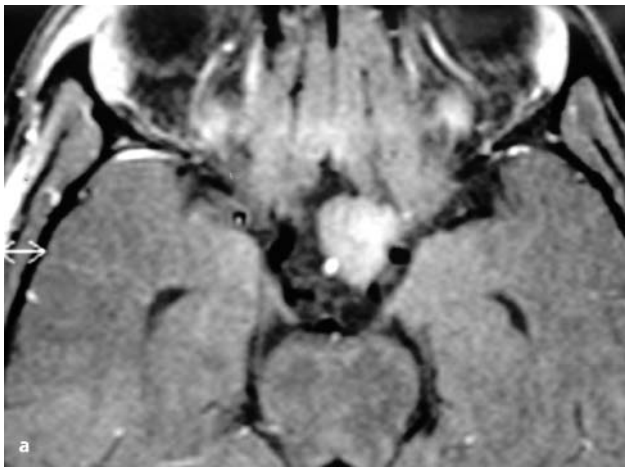
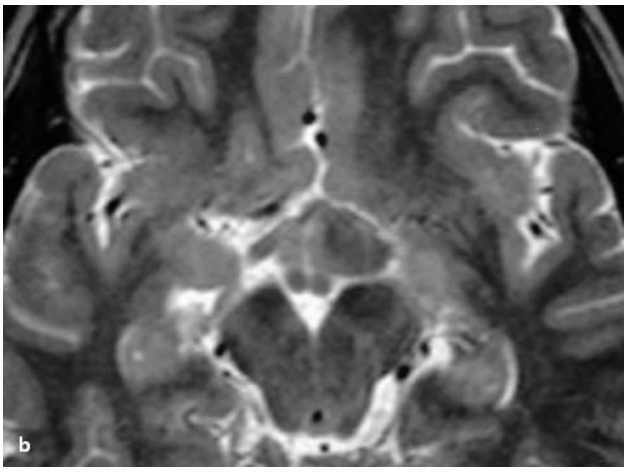


Fig. 22.2. **a** Microscopic view of an intra-axial optic nerve glioma (pilocytic astrocytoma) on the right side. **b** Intraoperative view after removal of the pilocytic astrocytoma and decompression of the optic nerve





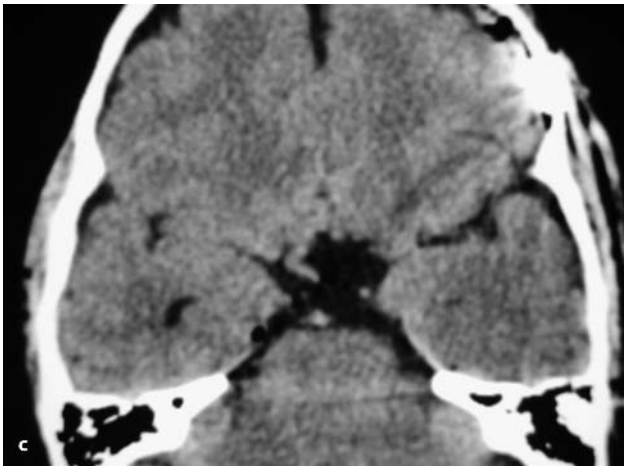
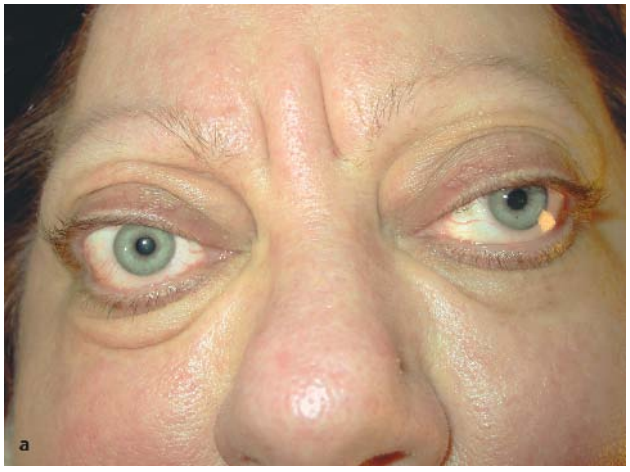


Fig. 22.3. **a** Intra-axial glioma of the chiasm and the optic tract (preoperative contrast-enhanced T_1-weighted axial MR image). **b** Preoperative T_2-weighted axial MR image of the same intra-axial glioma on the left side leading to almost complete ipsilateral visual loss. **c** Postoperative CT image after tumor removal. The ipsilateral optic tract had to be sacrificed to prevent infiltration of the contralateral side



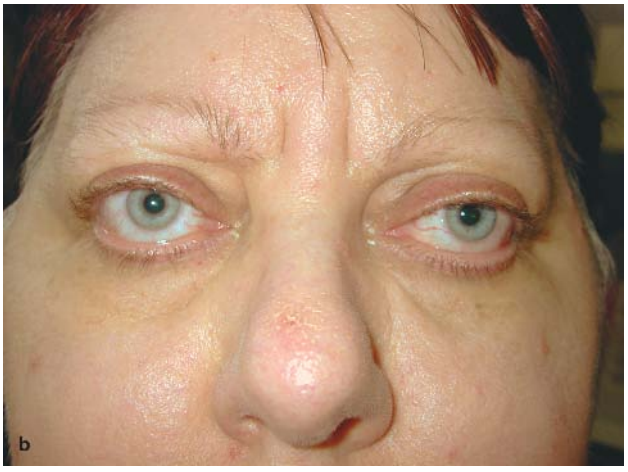


Fig. 22.4. Pre- and postoperative images (**a**, **b**) of a patient treated for endocrine orbitopathy

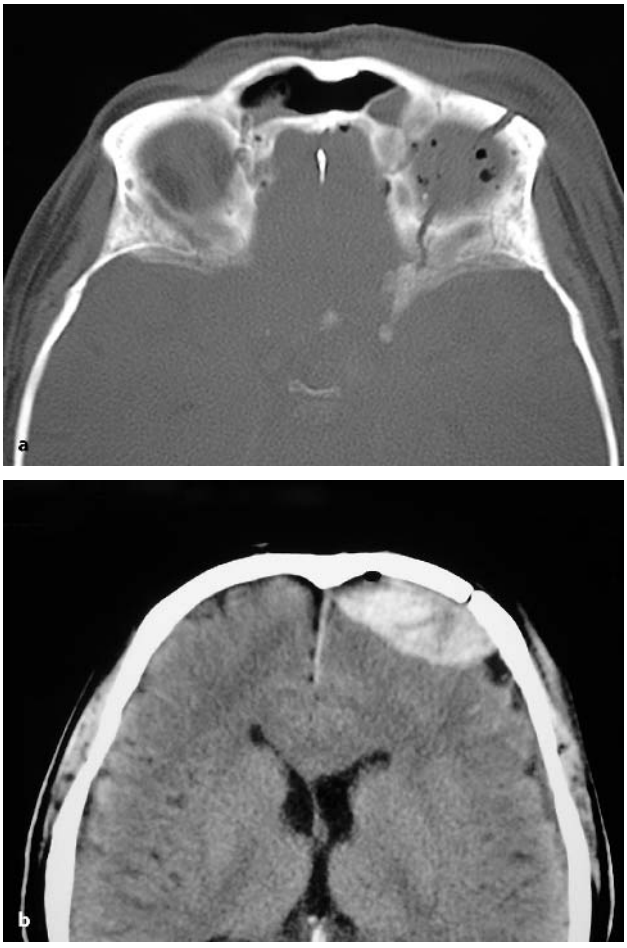


Fig. 22.5 CT images of a trauma patient presenting with a fracture of the orbital roof (**a**) with secondary visual deficit in the same side and an associated intracranial hematoma above the orbit (**b**). This constellation allows decompressing the orbit and evacuating the hematoma during one surgery

Anterior Skull Base Tumors

Meningiomas of the sphenoidal wing, the anterior clinoid, and the cavernous sinus may involve the optic canal and the superior orbital fissure (■ Fig. 22.6) as well as the intracranial optic nerves and optic chiasm.

! Note

Frontolateral or pterional craniotomies allow exposure and removal of these lesions with good functional outcome.

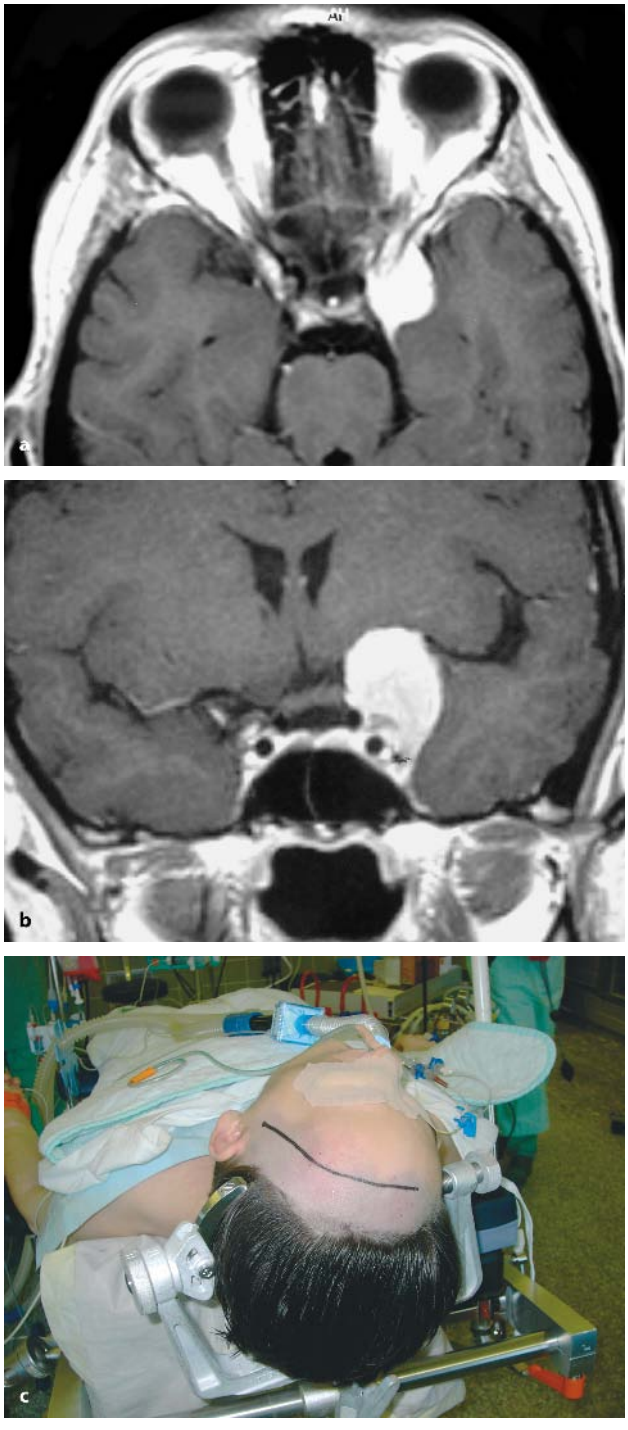


Fig. 22.6. Meningioma of the left clinoid process in axial (**a**) and coronal (**b**) planes of contrast-enhanced T_1-weighted MR images. Patient positioning and skin incision behind the hairline for a frontolateral approach to remove this lesion (**c**)

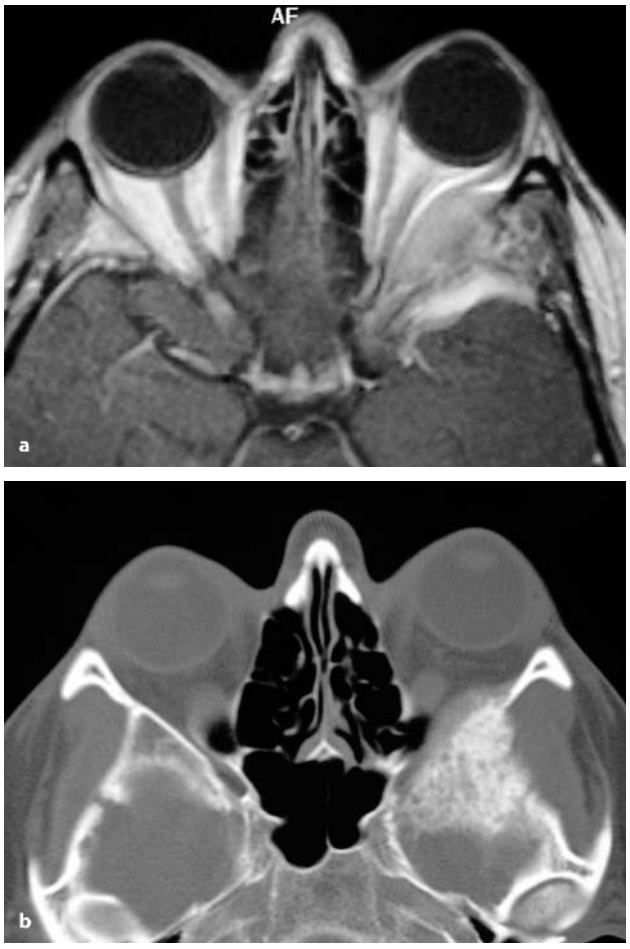


Fig. 22.7. Intraosseous sphenoid wing meningioma compressing and displacing the left optic nerve [preoperative contrast-enhanced T_1-weighted axial MR image (**a**) and bone-window CT image (**b**)]

Pearl

If the cavernous sinus is massively infiltrated, partial tumor removal is followed by stereotactic fractionated radiotherapy or radiosurgery. Radical removal of meningiomas from within the cavernous sinus has been used in the past, but has since been abandoned because of high morbidity and mortality and in particular, deterioration of oculomotor function.

When intraosseous meningiomas or fibrous dysplasia lead to hyperostosis and compression of the optic nerves, bony decompression is performed via a frontolateral or pterional approach using a diamond high-speed drill (■ Fig. 22.7).

Sellar and Parasellar Tumors

Definition

Pituitary adenomas are the predominating lesions of the sellar region. Hormone-secreting pituitary adenomas (i.e., prolactinomas, growth hormone [GH]-secreting adenomas, adrenocorticotrophic hormone [ACTH]-secreting adenomas) are often diagnosed by symptoms due to hormonal hypersecretion, and visual impairment is less frequent. In contrast, nonfunctioning pituitary adenomas only become symptomatic when a large space-occupying lesion develops (■ Fig. 22.8). Visual failure is the prevailing symptom of nonfunctioning pituitary adenomas. It is caused by suprasellar tumor extension.

Neuro-ophthalmological evaluation typically detects chiasmal syndrome. Early diagnosis and appropriate surgical therapy are crucial, as progression of chiasmal syndrome would ultimately result in blindness.

Note

The majority of pituitary adenomas can be removed by a transnasal, trans-sphenoidal approach (■ Fig. 22.9).

Total removal is feasible unless massive invasion of adjacent structures such as the cavernous sinus is found. Visual outcome of trans-sphenoidal surgery is favorable. Improvement of chiasmal syndrome or even total restoration of visual function is accomplished in up to 90% of the cases. Residual tumor within the cavernous sinus can be treated by fractionated radiotherapy or radiosurgery see Chap. 23. Only in those cases with massive intracranial extension and perforation of the diaphragma sellae does a transcranial approach have to be performed using a frontolateral or pterional craniotomy.

Definition

Craniopharyngiomas are also benign lesions of the pituitary and hypothalamic region and make up 1% of intracranial tumors. They occur both in childhood and in adult life. Craniopharyngiomas often show the typical triad with solid tumor, cysts, and calcifications (■ Fig. 22.10).

Chiasmal syndrome is frequently encountered. Surgical therapy of craniopharyngiomas is challenging. Total removal is only accomplished in 50% of cases, and craniopharyngiomas tend to recur. Removal is incomplete in the presence of severe hypothalamic involvement and extensive tumor size.

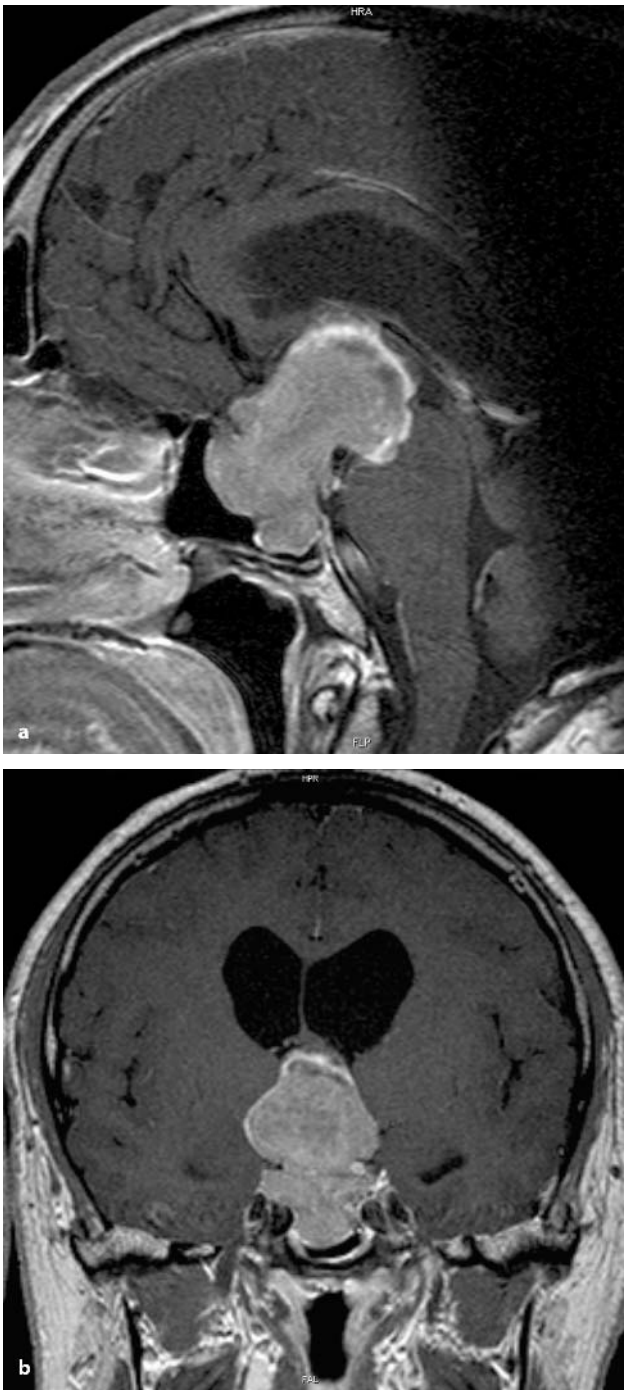


Fig. 22.8. Intra- and suprasellar pituitary macroadenoma with typical lobulated figure-of-eight or "snow man" appearance in sagittal (a) and coronal (b) contrast-enhanced T_1-weighted MR images

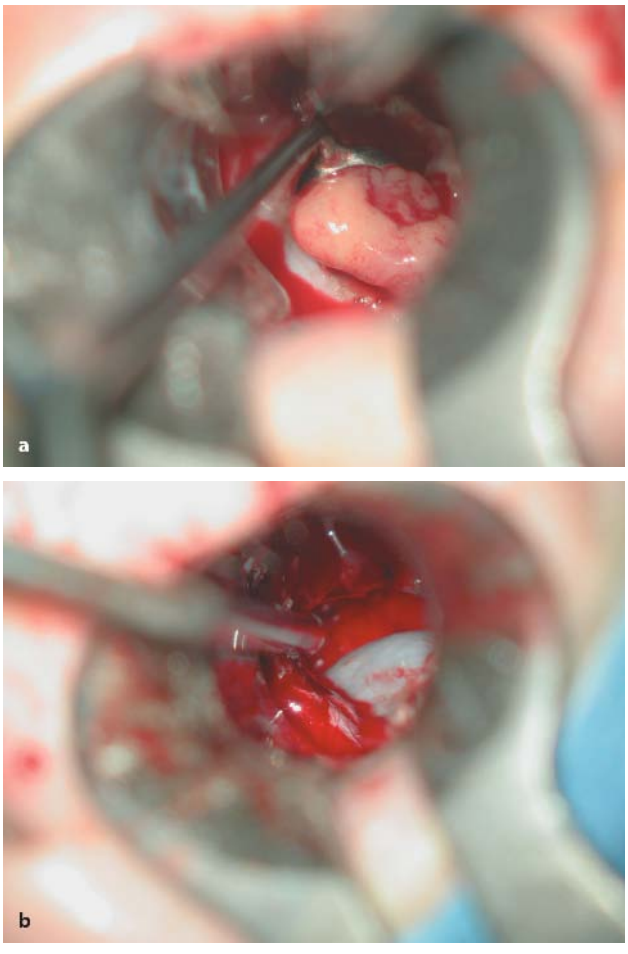


Fig. 22.9. Microscopic transnasal, trans-sphenoidal view of a pituitary adenoma before (a) and after resection (b), exposing the diaphragma sellae

Note

Only 30% of craniopharyngiomas can be removed by a trans-sphenoidal operation, while 70% of craniopharyngiomas have to be operated on by craniotomy. A frontolateral or pterional approach is most frequently used.

Some neurosurgeons prefer a bifrontal approach in the presence of major retrosellar extension. Decompression of the optic chiasm is accomplished in the majority of cases. Hence, most patients experience postoperative visual improvement. However, a rate of 10 to 15% of visual deterioration is encountered following transcranial tumor resections.

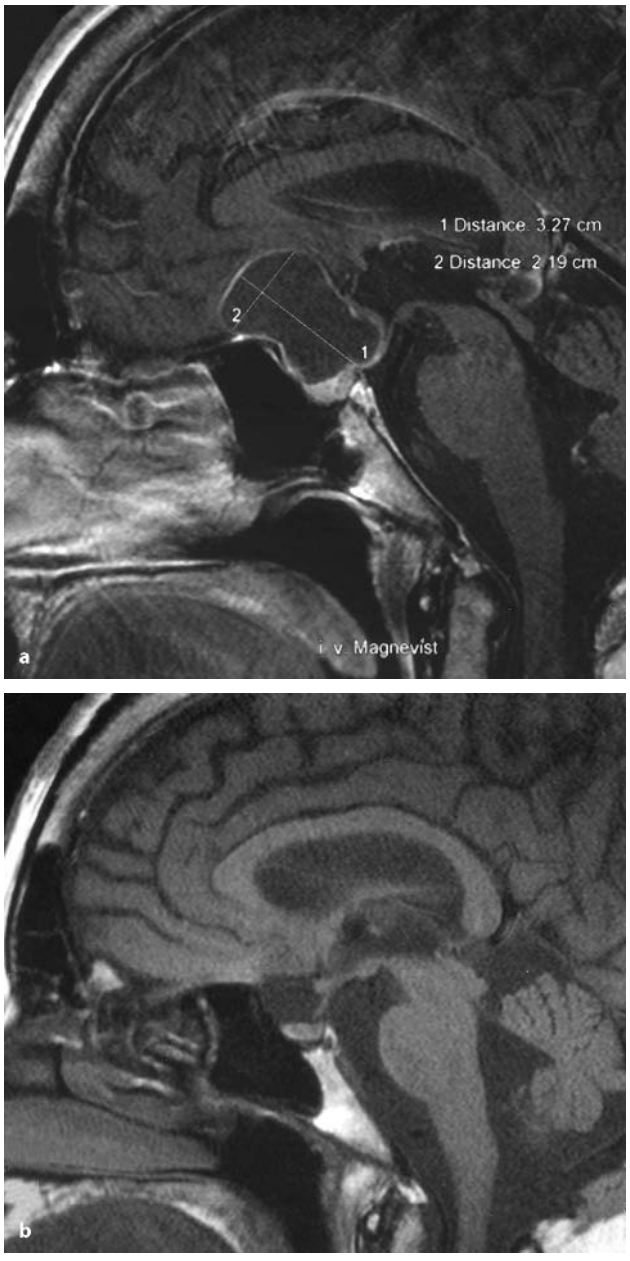


Fig. 22.10. Pre- and postoperative sagittal MR images (**a**, **b**) of a cystic craniopharyngioma that was completely removed via a transnasal approach

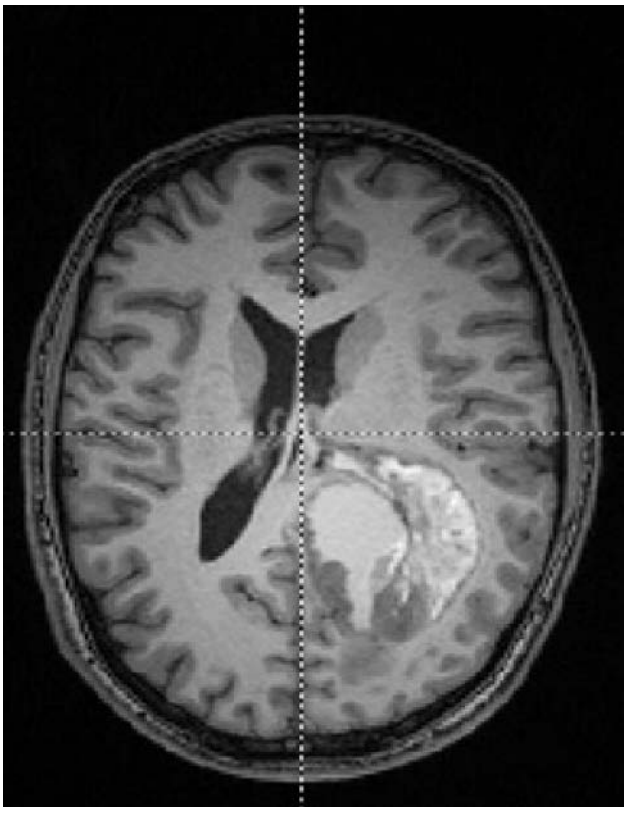


Fig. 22.11. Intracranial space-occupying lesion (ependymoma of the lateral ventricle) displacing the optic radiation laterally

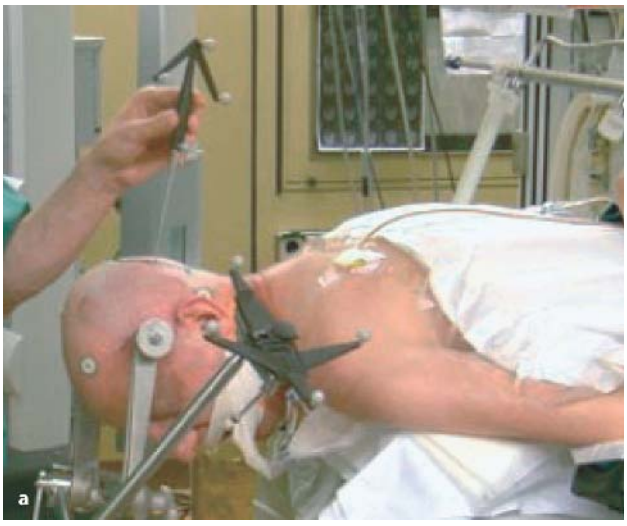
Hemispheric Tumors

Gliomas, metastases, and ventricular tumors like ependymomas may compromise the dorsal part of the visual system by displacing or infiltrating the optic radiation (■ Fig. 22.11). These lesions are often approached via a craniotomy of the skull in the direct vicinity of the lesion.

Pearl

Image-guidance techniques help to localize the less invasive trans-sulcal or interhemispheric approach (■ Fig. 22.12). On the other hand, the operative approach has to avoid critical areas, e.g., speech area or optic radiation (■ Fig. 22.13). Recent technological innovations allow imaging of the optic radiation fibers using special MRI sequences (diffusion tensor imaging [DTI]), thereby facilitating the preservation of these structures (see also "Technology" section [■ Fig. 22.21]).

Intraoperatively, direct electrophysiological stimulation of these fiber tracts may help to confirm these imaging findings, thereby increasing the safety of the procedure (see also "Technology" section [■ Fig. 22.20]).



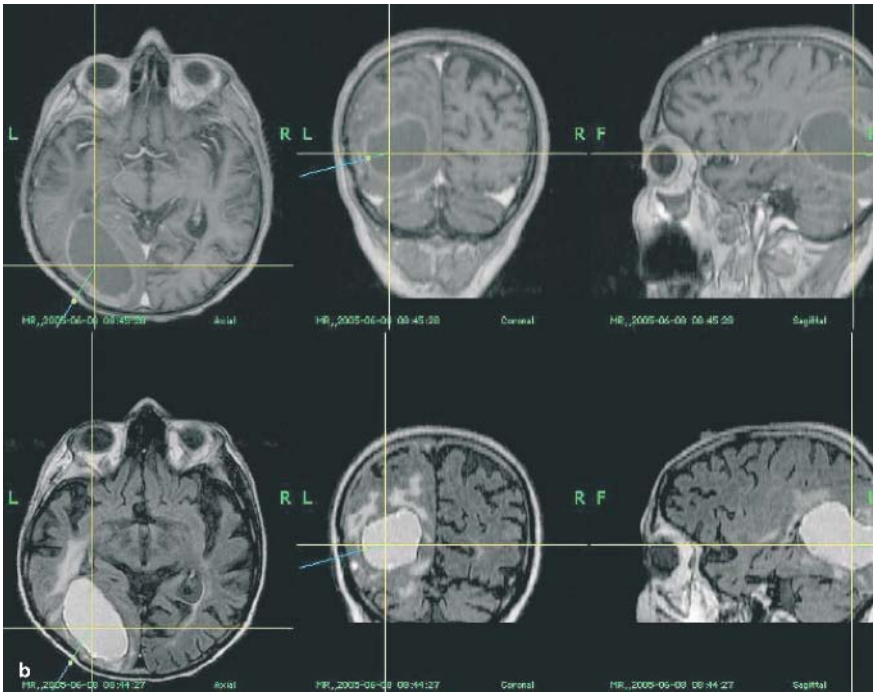


Fig. 22.12. Image-guided planning of a craniotomy in the vicinity of a hemispheric occipital lesion. The surgeon uses a handheld pointer with infrared light-emitting diodes (**a**) that are detected by the camera of the navigation system. The location of the pointer tip is indicated on the monitor of the navigation system in relation to the patient-specific MR images of a cystic metastasis (**b**) in triaxial planes (contrast-enhanced T_1 and flair-weighted T_2 images)

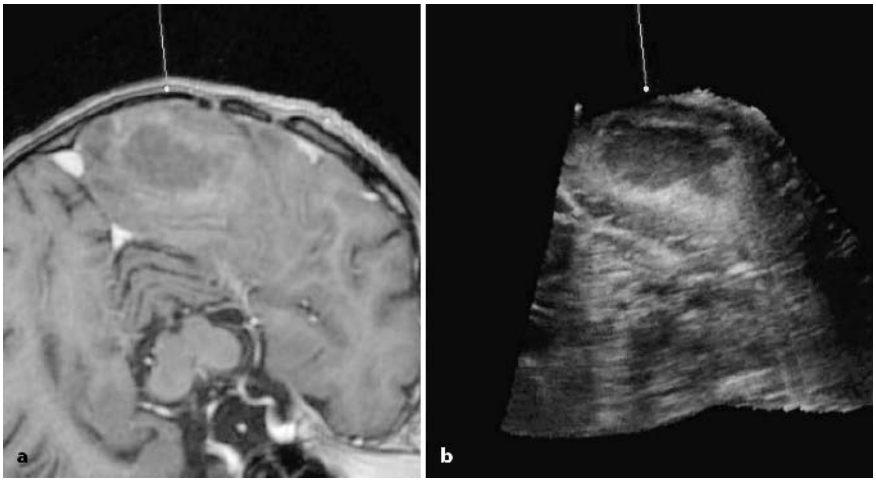


Fig. 22.13. Image-guided planning of the operative trajectory to avoid critical areas, e.g., optic radiation. Online visualization of preoperative MR (**a**) and intraoperative ultrasound images (**b**) allows compensation for brain shift during resection of the cystic metastasis

Preoperative Workup

The neurosurgeon has to base the decisions concerning the treatment strategy on the sum of information accessible. The ophthalmologist will support this process by contributing the following facts: When was the onset of ophthalmologic symptoms, and what was their course since then? What are the current neuro-ophthalmologic findings like visual acuity and visual field deficits? Is oculomotor function impaired, and which motor nerves are involved? Does the optic disc show any signs of atrophy or papilledema? Which topographic conclusions in terms of the probable side of compression of the visual pathway can be drawn from these findings? Are there any additional neurological findings, e.g., indicating the involvement of other cranial nerves? Furthermore, all available imaging findings, as detected by modern magnetic resonance and computer tomography imaging, are included in decision-making.

Note

Today, the nature of the pathology can be determined preoperatively with a high degree of accuracy.

Is a recent internal medicine evaluation available indicating the patient's suitability for surgery and concomitant risk factors?

Operative Technique

Pearl

The treatment strategy depends on the biological nature of the pathology. In benign tumors, the surgeon intends to remove the tumor completely while seeking optimal preservation of function. In these cases, the resection often follows a transtumoral approach, reducing the size of the lesion in a piecemeal fashion.

En bloc resection is a surgical principle in the treatment of malignant tumors. Malignant tumors demand an en bloc resection that includes healthy tissue around the lesion. In these cases, the indication for operation depends on the possibility to resect the lesion radically, including the necessity to sacrifice vision on one side.

However, en bloc resection is mostly not feasible in intracranial, intra-axial lesions. In glioma surgery, curative surgery is not possible because of the infiltrative nature of the tumors. The aim of surgery is the removal of visible tumor while preserving function. Postoperatively, adjuvant radiotherapy and/or chemotherapy are necessary. Radical resection is not performed when sacrifice of vision does not reflect cure or significant increase of life expectancy, and when the tumor is invading the cavernous sinus. If the tumor is infiltrating the surrounding structures but shows a slow growing pattern, a partial removal is performed with the aim of decompressing the visual pathway in order to maintain the quality of life.

Extracranial Approach

Tumors of the paranasal sinuses, several intraorbital lesions, and sellar tumors can be accessed via extracranial approaches.

Transorbital Approach

Both malignant and benign tumors of the anterior skull base and paranasal sinuses that compress structures of the visual system but do not show any intradural extension can be exposed via different orbitotomies, depending on their localization in relation to the optic nerve (■ Fig. 22.14).

Note

Extended bone infiltration necessitates a fronto-orbital approach with resection of the osseous skull base (■ Fig. 22.15). The intraoperative orientation is provided by anatomical landmarks, e.g., superior orbital fissure, optic foramen, foramina ovale, and rotundum. When the underlying dura mater is infiltrated, it will be resected and replaced as well.

Definition

The **extent of surgical tumor removal** in meningiomas can be classified according to the Simpson grading system, from macroscopically complete removal with excision of dural attachment and abnormal bone (grade I) to simple decompression (grade V).

Pearl

The transconjunctival approach is a useful way with good intraoperative visibility, especially for lesions located in the inferior medial and basal compartment of the orbit. Deep intraconal lesions at the orbital apex and extraconal superior lesions are less accessible by this approach. However, selected intraorbital lesions may be resected without muscle dissection, leading to excellent cosmetic and functional results.

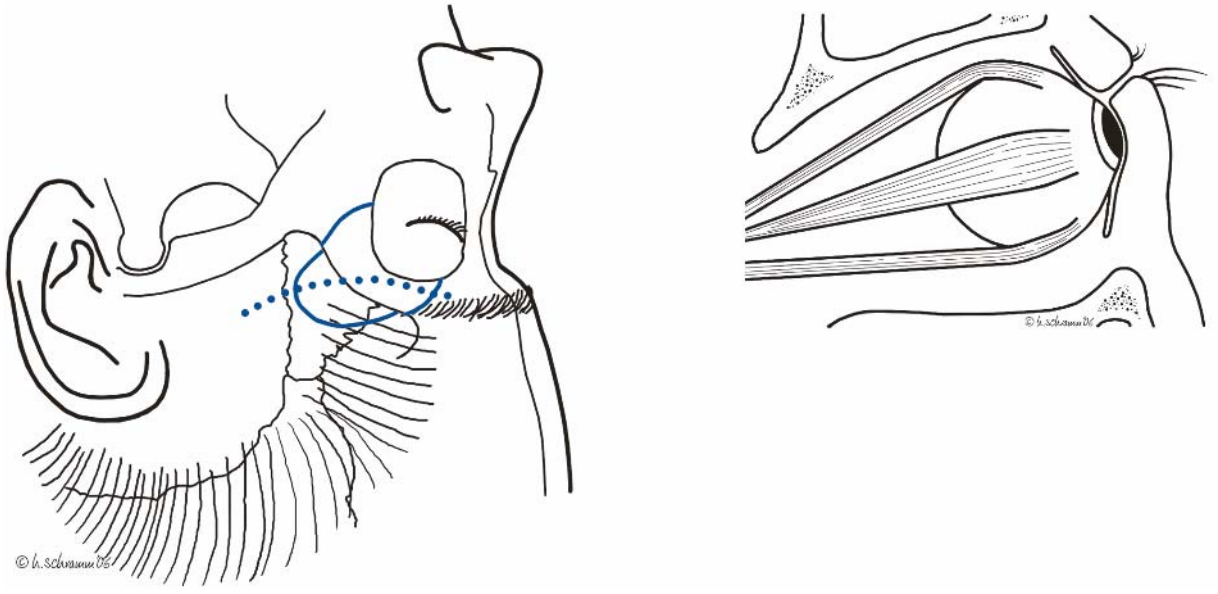


Fig. 22.14. Skin incision and bone removal for a lateral orbitotomy, exposing the orbital contents

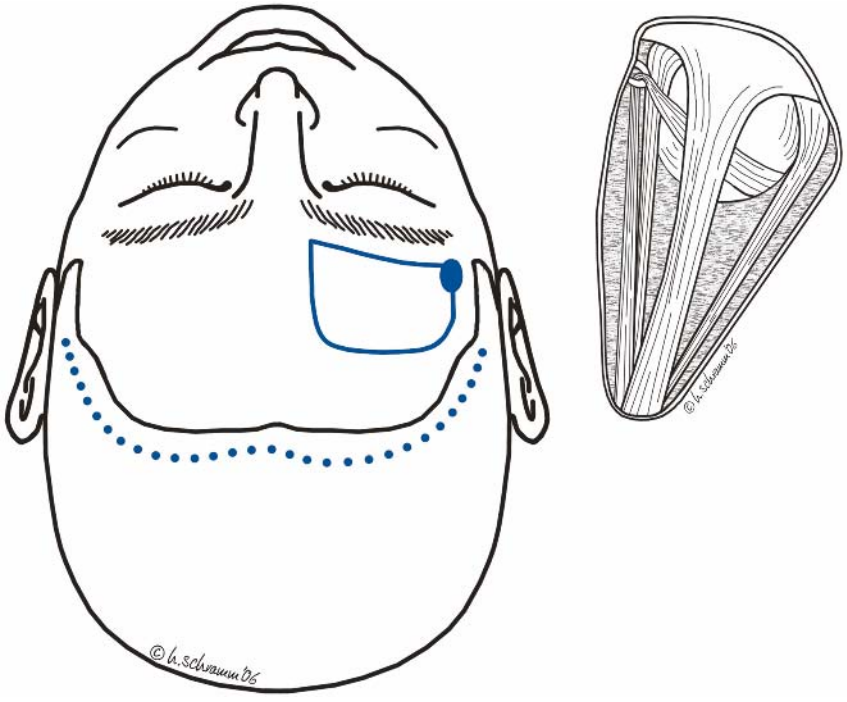


Fig. 22.15. Bicoronal skin incision and location of burr holes for a fronto-orbital approach. The *straight line* shows the location and the size of the bone removal

Trans-Sphenoidal Approach

Note

More that 95% of pituitary adenomas and most adenomas with suprasellar extension can be removed via a transnasal, trans-sphenoidal procedure.

Classically, a trans-septal, submucosal approach was performed. Today, most pituitary surgeons prefer the direct pernasal approach to the sella. With this technique, the nasal septum is disconnected from the sphenoid and displaced laterally with the speculum. The direct pernasal approach is minimally invasive. It avoids major dissection of the nasal septum, and it is well tolerated by the patients, with minimal postoperative discomfort and minimal nasal swelling (■ Fig. 22.16).

Pearl

Today, extended trans-sphenoidal approaches are available and provide access not only to the pituitary fossa, but also to the clivus, posterior ethmoid, cavernous sinus, and suprasellar area. Decompression of the optic nerves and optic chiasm as well as decompression of the oculomotor nerves within the cavernous sinus is accomplished. The extended trans-sphenoidal approach allows not only removal of extensive adenomas, but also removal of other pathologies such as perisellar metastasis or chordomas.

For example, skull base chordomas frequently produce abducens nerve paresis that recovers after trans-sphenoidal tumor removal. Trans-sphenoidal surgery is performed with microsurgical techniques. Today, selective adenomectomy is performed, with preservation of pituitary function.

Note

Modern technical tools enhance tumor removal and minimize the complication rate. Parasellar and suprasellar tumors are directly visualized and removed with the use of endoscopes. Neuronavigation systems are used in extensive lesions to avoid injury to the carotid artery and provide intraoperative orientation.

The complication rate of trans-sphenoidal surgery is low. In experienced centers, the frequency of meningitis and cerebrospinal fluid rhinorrhea, which are typical complications of trans-sphenoidal procedures, is below 1%.

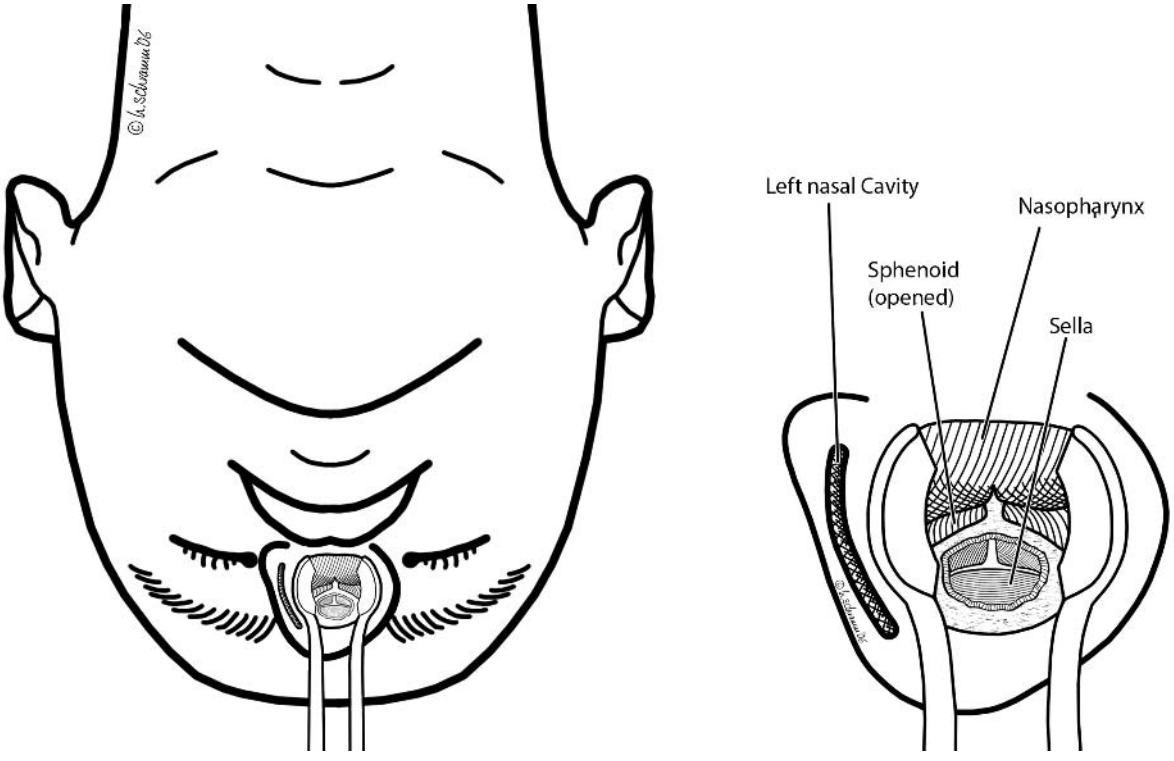


Fig. 22.16. Transnasal, trans-sphenoidal access to the sella, using a trans-septal, submucosal approach. The nasal septum is disconnected from the sphenoid and displaced laterally with the speculum

Intracranial Approach

If tumors of the anterior skull base are located primarily extradural, they can be visualized by elevating the dura without the necessity to open it. Intradural tumors, e.g., meningiomas, have to be exposed by opening the dura via either a bifrontal or a unilateral frontal craniotomy.

Extradural Approach

Extradural frontal approaches can be performed using a bilateral or a unilateral craniotomy, depending on the size of the lesion to be removed. The optic canal and the superior aspect of the orbital contents can be visualized by this approach, while the optic chiasm and the intradural optic nerve cannot.

Intradural Approach

In addition to the intradural frontal approach, both uni- and bilateral craniotomies are possible.

Pearl

In recent years, the unilateral frontolateral craniotomy is preferred because of less invasiveness and sufficient exposure of the anterior cranial base and the suprasellar region. The skin incision is hidden behind the hairline. The small flap is located close to the floor of the cranial base, allowing exposure of both optic nerves and the chiasm.

This approach is preferred for lesions of the anterior visual system (■ Fig. 22.17). It can be performed for sphenoidal wing meningioma, meningioma of the anterior clinoid, and suprasellar tumors.

For the exposure of the parasellar area, the frontotemporal craniotomy often becomes necessary with retraction of the temporal muscle (■ Fig. 22.18).

Technology

Definition

Several **technical innovations** like image-guidance systems, computer simulations, three-dimensional image renderings, and intraoperative monitoring allow the neurosurgeon to precisely localize lesions and evaluate their extent in relation to adjacent neural structures, and determine their functional integrity by electrophysiological means. This combined approach improves patient safety.

Neuronavigation

Preoperative CT and MR images can be used for surgical planning and intraoperative orientation when using neuronavigational systems. These devices are based on the principle of frameless stereotaxy, and they allow for image guidance during surgery. The target localization accuracy of these tools reaches a precision of up to a few millimeters.

Pearl

A major limitation of navigational systems that work with preoperative images is that of intraoperative shifts in brain position. This problem is minimal during skull base surgery. Therefore, this technique is most appropriate to define target trajectories and to plan the surgical approach with custom-tailored craniotomies when removing lesions of the skull base near the visual system.

During frontolateral craniotomies, for example, image guidance helps to avoid an unintended opening of the frontal sinuses by visualizing these structures prior to skin incision and craniotomy. In hemispheric lesions, neuronavigation is most helpful to determine the exact location and extent of the lesion prior to skin incision and craniotomy (■ Fig. 22.19).

Intraoperative Monitoring

Continuous monitoring of nerve function is possible during surgery. The immediate feedback of the electrophysiological response allows the neurosurgeon to adjust his microsurgical technique to the current functional status of the manipulated structure. The integrity of the visual pathway can be monitored measuring visually evoked potentials at the occiput. Changes of latency and amplitude of these electrophysiological signals help to detect slightest disturbances during surgery. This technique is very susceptible to artifacts, when other electrical systems and machines are in use.

Pearl

More recently, intraoperative stimulation of white matter tracts can be applied by using subcortical electrical stimulation to induce evoked potentials. When the patient is awake, even phosphenes can be induced using this technique. Whenever these responses are evoked during iterative stimulation, tumor resection has to be interrupted in order to preserve the functional integrity of the optic radiation (■ Fig. 22.20).

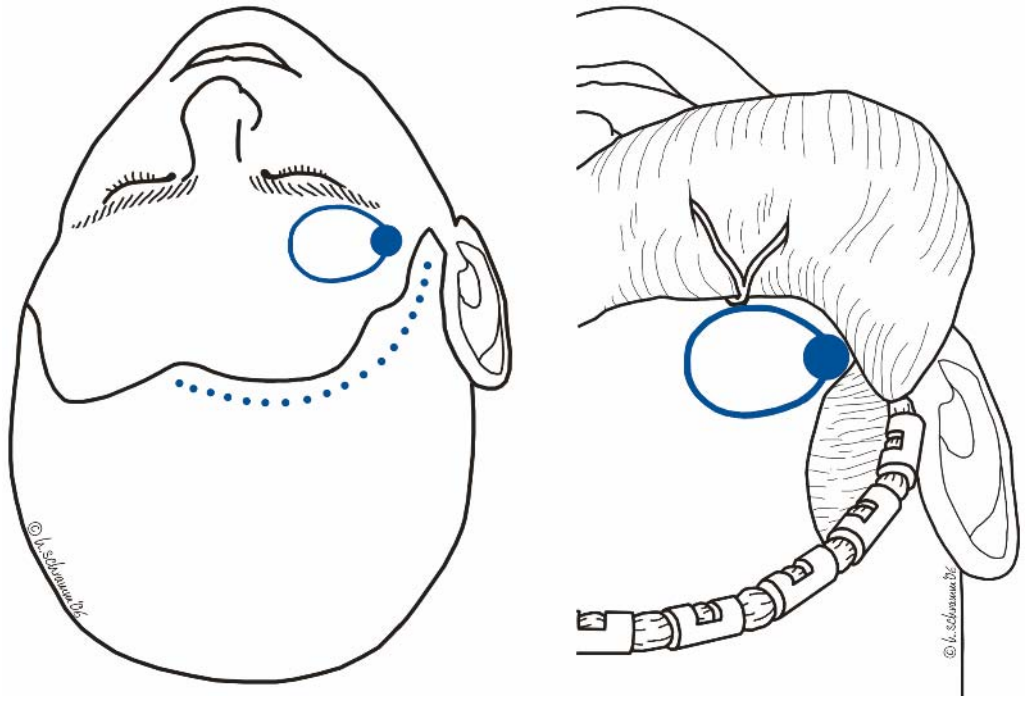


Fig. 22.17. Head positioning and skin incision for the frontolateral approach. The *straight line* shows the location and the size of the craniotomy

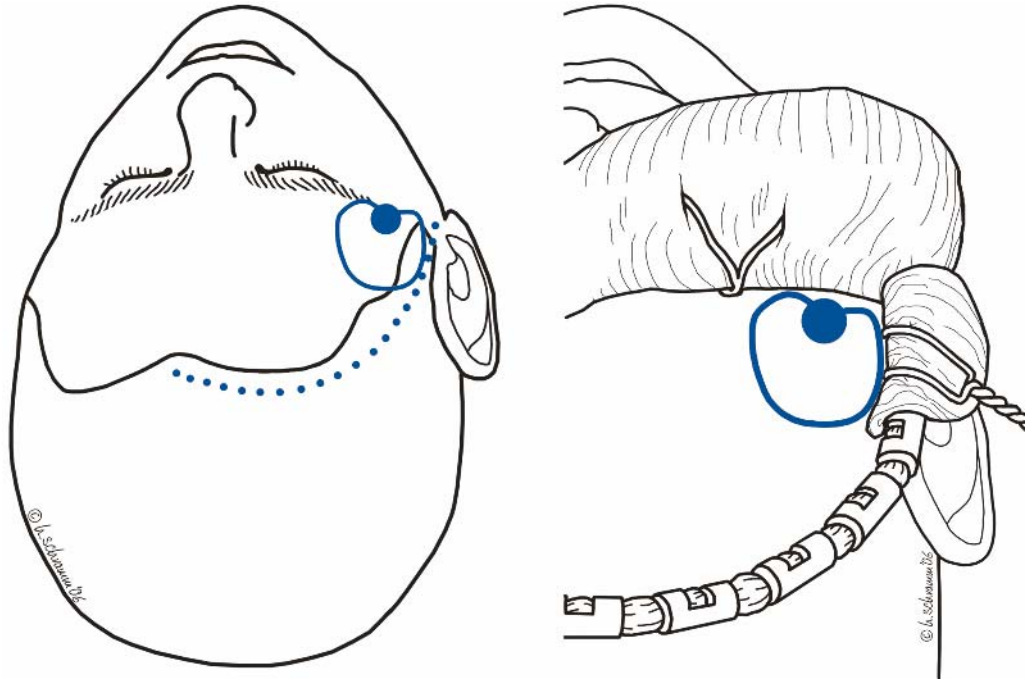


Fig. 22.18. Head positioning and skin incision for the frontotemporal approach. The *straight line* shows the location and the size of the craniotomy

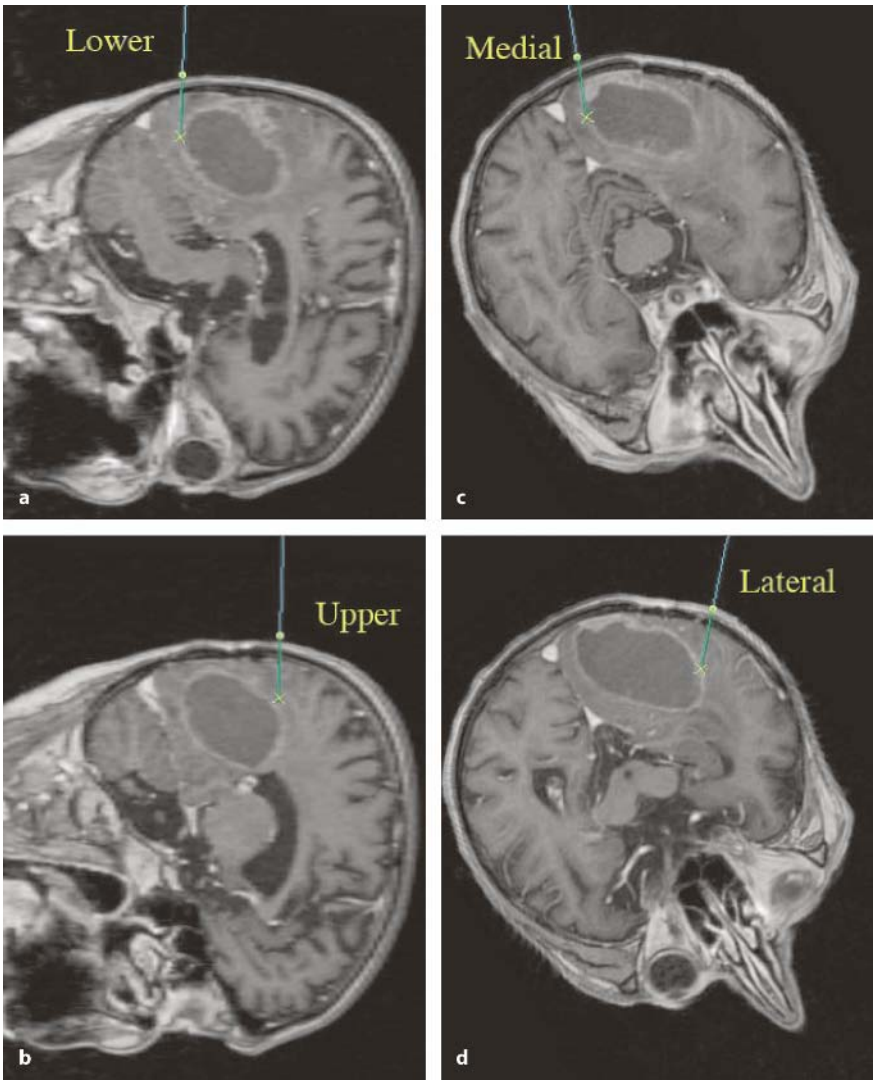


Fig. 22.19. Image-guided localization of an intracranial lesion of the occipital lobe. The lower (**a**), upper (**b**), medial (**c**), lateral (**d**) edge of the tumor can easily be projected on the skin surface to plan a custom-tailored approach

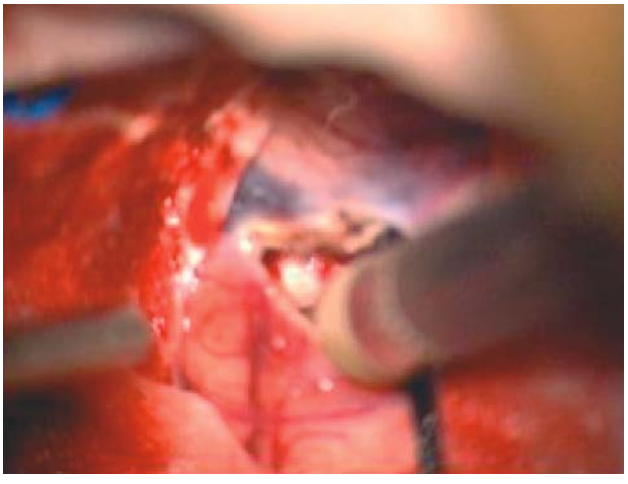


Fig. 22.20. Intraoperative direct electrical stimulation of the subcortical white matter tracts of the visual pathway will limit the extent of tumor resection whenever eliciting phosphenes/visually evoked potentials

Imaging

Modern imaging techniques allow acquiring a huge amount of additional information to plan the strategy and extent of tumor removal.

! Note

With surgical MRI units or with navigated ultrasound systems, even an intraoperative update of the imaging information is possible.

This allows for compensating the brain shift during the procedure. For many years the anterior parts of the visual system up to the lateral geniculate body could be visualized with classical imaging sequences but the optic radiation and the visual cortex could not be delineated as precisely as necessary for surgical planning.

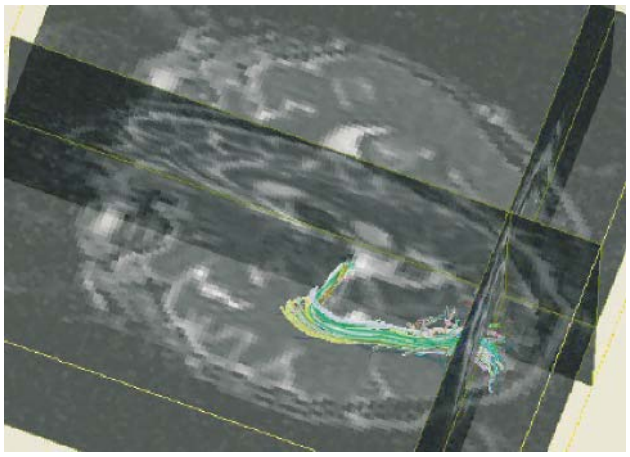


Fig. 22.21. Visualizing the optic radiation by MR diffusion tensor imaging (DTI)-based tractography

Pearl

Functional magnetic resonance (fMRI) and DTI are recent and innovative modalities that allow visualization of both the cortical and the subcortical structures of the posterior part of the visual system in detail. In particular, the optic radiation can now be localized, when planning the surgical approach to hemispheric, periventricularly located lesions (■ Fig. 22.21).

Conclusion

Optimal management of intra- and extra-axial lesions of the visual pathway can be provided when an interdisciplinary team cooperates closely during the diagnostic and treatment process. The ophthalmologist, who is confronted first with these patients plays an important role initiating the proper course of action based on an intimate understanding of the treatment philosophy and management algorithms of the multi-specialist team.

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Chapter 23

Radiotherapy for Tumors of the Anterior Visual Pathway

G. Becker, R.-D. Kortmann, and H. Wilhelm

Tumors of the anterior visual pathway are almost without exception benign. However, this does not mean that they are radiation insensitive. This is true for pituitary adenomas as well as for meningiomas. For the latter type, radiation therapy is a valid alternative treatment when complete excision is impossible or would be complicated by high morbidity.

Side Effects of Radiation Therapy

Radiation therapy of the anterior visual pathway has long been used with a certain degree of reluctance, since the side effects are potentially disastrous. For many years, it was believed that radiation therapy of optic nerve tumors was of little use, since the healthy portions of the nerve had practically the same radiosensitivity as the tumor. The risk of bilateral radiation optic neuropathy and total blindness prevented even consideration of radiotherapy as a valid choice for treatment. In addition, if the globe lay within the field of treatment, the risk of a radiation retinopathy and/or cataract were additional possibilities. If the tumor was located close the pituitary gland, endocrinopathies were also possible. ■ Table 23.1 lists the critical radiation doses for the various structures in and around the anterior visual pathway.

Table 23.1. Critical dosage thresholds

Target tissue	Dosage (Gy)
Optic nerve	54
Retina	45
Lens	10
Lacrimal glands	32
Pituitary gland	25–30

Three-Dimensional Planning of Radiotherapy and Conformational Irradiation

Three-dimensional planning of treatment has led to a significant reduction in the side effects of radiotherapy, as compared with the classic two-dimensional method. The advent of computed tomography and magnetic resonance imaging has also allowed improvements to be made in the use of radiation as a therapeutic medium. The basis for calculation of volumetric dosing of radiation has paralleled the development of stereotactic methods of neurosurgery. The computational process is similar, but the tumor, rather than being imaged, is exposed to gamma or X-rays. The tumor is computationally located, and then the "virtual" tumor is irradiated by an instrument that uses the same pattern. This process is referred to as conformational dosing, a method that spares surrounding normal tissues to a maximal extent; the contralateral optic nerve is now largely spared. Focused stereotactic targeting allows a highly precise delivery of radiation. For this method a mask is prepared, so that no significant inaccuracies can result from inadvertent movements or changes in body position (■ Fig. 23.1). The accuracy of the method has a precision of 1 to 2 mm.

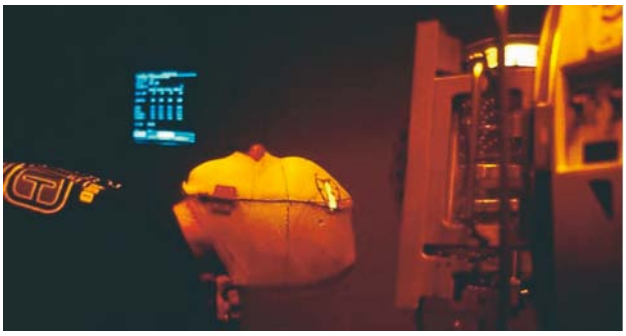

Fig. 23.1. Patient fitted with mask for application of stereotactically guided conformational irradiation

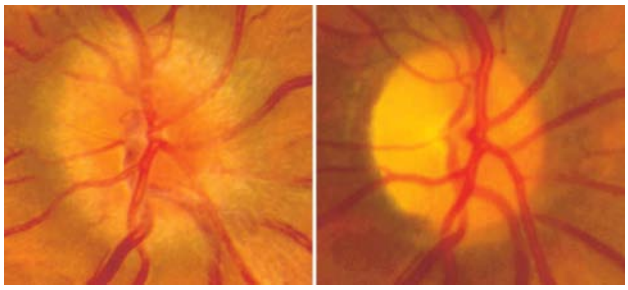

Fig. 23.2. Regression of optic disc edema in a patient with an optic nerve sheath meningioma after fractionated, stereotactically guided, conformational irradiation

Radiosurgery and Fractionated Irradiation

There are two primary methods for the use of radiation therapy, radiosurgery, in which the total dose of radiation is administered in a single session, and fractionated irradiation, in which the total dose is given over a period of several sessions. In the case of a meningioma, this may be as many as 30 separate sessions. Radiosurgery has the inherent risk of a high single dose causing damage to healthy tissues, even though the total dose of radiation is within an acceptable range. Experience has taught us that for the production of radiation optic neuropathy, single dosing often plays an important role. If the total single dose remains less than 2 Gy, optic nerve damage is very unlikely.

Pearl

As a general rule, when seeking to retain function, fractionated application is preferred.

This is radiobiologically more favorable, since the tumor cells can partially recover between the single sessions and begin to divide again, increasing their susceptibility to the radiation effect.

Indications for Radiation Therapy

Radiation therapy is indicated when surgical removal of a tumor is incomplete or when growth of the neoplasm recurs following surgical excision. This applies not just to pituitary adenomas, but also to meningiomas and gliomas (■ Fig. 23.2). Primary tumors of the optic nerve or its meningeal sheath cannot be surgically removed without also sacrificing visual function. Radiation therapy for meningiomas can usually be expected to stop further growth, and will often improve visual function, even though the tumor shows no reduction in size on CT or MRI images. It is likely that the number of useful applications for radiation oncology will continue to expand in coming years.

Conclusion

Radiation therapy plays an increasingly important role in the treatment of benign tumors of the anterior afferent visual pathway, due primarily to the evolution of stereotactic methods that allow some degree of protection for healthy tissues while either shrinking the size or preventing further growth of neoplasm. It can be expected that the indications for this type of therapy will continue to expand.

Further Reading

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Chapter 24

Reading Disorders

S. Trauzettel-Klosinski

The ability to read is a basic necessity of modern societal organization. Whether printed or on a monitor, our most important source of information is the printed word. Reading is one of the most important skills of daily living, and loss of reading ability results in increased dependency, poor communication, poor employability, decay of mental agility, and reduced quality of life. Reading is a complex sensorimotor cognitive function that can be damaged at many different levels.

Physiologic Foundation of Reading

The optical tissues of the eye ensure the formation of a well-focused and complete image of text onto the retina. Refractive errors and loss of accommodation are easily compensated for by use of appropriate spectacle corrections. For the legibility of newsprint at a distance of 25 cm (10 in.), an acuity of about 20/50 or better is required.

The resolving power of the retina drops rapidly with increasing eccentricity (■ Fig. 24.1). Visual acuity, however, is not an adequate measure for the ability to read, since acuity tests measure the ability to recognize correctly individual alphanumeric characters, one at a time.

Pearl

During fixation at some point in a line of print, a group of adjacent characters are seen, an ability that requires a minimum breadth of visual field of about 2° to either side of the locus of fixation and 1° above and below.

The total area of perception during fixation can actually extend significantly beyond these limits, up to about 5° in the direction of reading (i.e., to the right). This ability allows for a type of parafoveal sensory input that makes several words (up to 15 characters in reading direction) visible at a single glance (■ Fig. 24.1). This area of the central visual field has been called the perceptual span for reading.

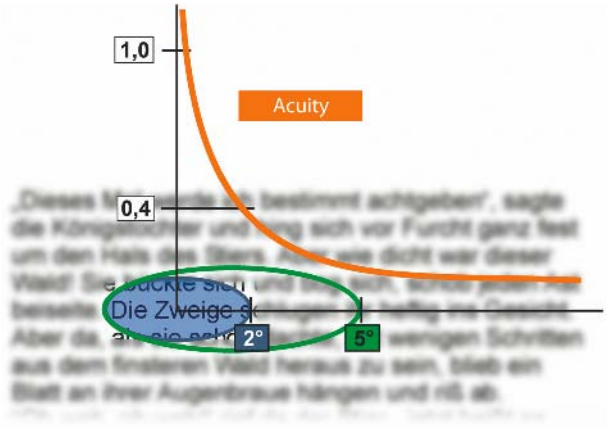


Fig. 24.1. Acuity as a function of eccentricity, minimum size of the reading visual field, and total perceptual span, as mapped onto a passage of text: Acuity falls sharply with increasing eccentricity. To read newsprint at a distance of 10 in., an acuity of 0.4 (20/50) is required; the minimum size of reading visual field (shown in *blue*) amounts to 2° to the left and right of fixation and 1° above and below fixation. Text is clearly legible in this region only. Total perceptual span during a moment of fixation (shown in *green*) can be extended up to 5° in the direction of reading

To recognize correctly the next group of letters, a precise saccade in their direction is required. During fluent reading, a regular sequence of saccades and fixational pauses is regularly interrupted by a return sweep back to the start of the next line of print. Recordings of eye movements during reading tasks produce typical staircase patterns.

The total area of retina used for reading is contained within a few square millimeters, but is represented at the visual cortex by a much larger proportion of neural tissue (neurosensory magnification). The central 10° of visual field, which correspond to about 2% of the entire visual field, is processed by a contiguous volume of more than half of the primary visual cortex. The perceived portion of text is transposed in the angular gyrus (the "reading center") into a phonetic form that is then further processed within a "sensory speech center" (the Wernicke region). Additional centers of brain cortex participate in the processing of the linguistic input, depending on the precise nature of the task, but that subject is beyond the scope of this book.

Reading Disturbances: Overview and Differential Diagnosis

The ophthalmologist is often the first professional sought out by patients with reading problems. An initial ophthalmic evaluation should include a detailed history of the patient's family, personal, ophthalmic, and scholastic history. This information allows for a correct classification of the reading problem and indicates the appropriate path for its further investigation (see flow diagram).

Ocular Sources of Reading Problems

If a child complains of asthenopic problems (headache, tearing, blurring, etc., during close work) or tells an adult that he/she has recently had problems with reading, the following ocular sources of reading problems should be either identified or ruled out:

- Optical problems: uncorrected refractive errors, in particular hyperopia, poor accommodative amplitude (presbyopia in midlife, poor accommodation in children), and clouding of the ocular media
- Sensory disturbances of reading: caused by problems of binocularity (heterophoria, strabismus, convergence insufficiency) or visual field defects within 5° of eccentricity (in this context, ocular sources of reading problems include lesions of the afferent visual pathways). Given the great importance of reading problems, caused by visual field defects, particularly in neuro-ophthalmology, these are discussed below in more detail.
- Motor disturbances of reading: both infra- and supranuclear disturbances of ocular motility and gaze control.

Specific and Isolated Reading and Spelling Problems, also Referred to as Developmental Dyslexia

Definition

Developmental dyslexia is an isolated disturbance of reading and writing in someone of normal intelligence and adequate schooling, with no accompanying deficits (whether sensory, motor, or psychological).

The patient's history can yield valuable clues: The problem has been present since the beginning of study of reading and writing. The parents report school problems, in particular poor grades in English, while the remaining subjects of school study are initially unaffected.

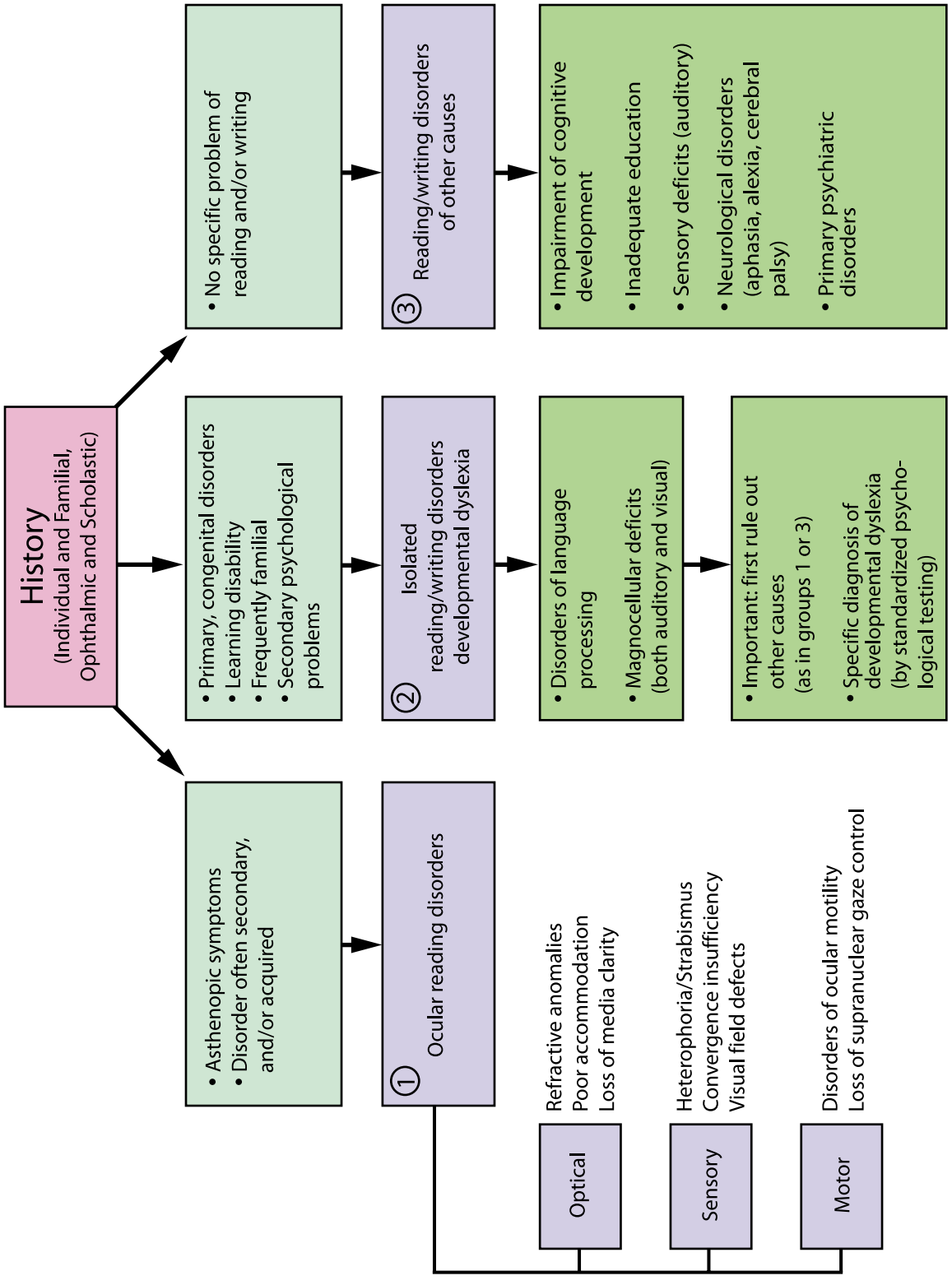
Characteristically, there are problems with reading (both in the understanding and fluency of reading) and writing, including the improper spelling of words in multiple forms in a single passage of text, transposition of sequences of letters, confusion with symmetrical letters (*q* with *p*, and *d* with *b*), and confusing similar sounding consonants (e.g., *d* with *t*). It is not so much the type of error that is important, but rather the frequency with which errors are made.

Occasionally, a family history of similar problems is reported, and there often are secondary psychological problems consequently.

Developmental dyslexia has been attributed to a disorder of language processing, which is often characterized by an impairment of the conversion of alphabetical characters into the phonetic elements of language, and by a deficit in phonological awareness. In addition, there are indications of deficits in the magnocellular auditory and visual pathways, resulting in poor processing of rapidly flowing sequences of stimuli.

The responsibility of the ophthalmologist is to rule out a primary ocular source of the reading problem, to treat any associated disorders, such as refractive anomalies (particularly high hyperopia and high corneal astigmatism) and strabismus (which is itself never a cause of developmental dyslexia), and to lay the foundation for a complete diagnostic study of possible causes: poor cognitive abilities, inadequate schooling, visual and auditory deficits, neurological diseases, and primary psychiatric disorders.

In addition, the ophthalmologist should arrange for a specific diagnostic evaluation of developmental dyslexia, based on standardized testing procedures. As a rule, these tests are best administered by psychologists or pediatric psychiatrists that are already familiar with the details of such clinical tests.



Flow diagram. Diagnostic procedures for reading disorders

A more extensive description of developmental dyslexia and its differential diagnosis by the ophthalmologist can be found in other works (see Trauzettel-Klosinski et al. 2002, 2003, under "Further Reading").

Reading and Writing Deficits of Other Causes

When taking a history, the physician may find that the problem is not limited to reading and writing. There can be other sources of trouble: poor aptitude, inadequate schooling, up to and including illiteracy, auditory deficits, neurological diseases (aphasia, alexia, cerebral palsy), and/or primary psychiatric disorders (psychoses and severe neurotic disorders).

Pearl

Such problems are usually unearthed during very careful history taking, and their discovery will generally lead to an appropriate plan for management.

Reading Disorders Caused by Visual Field Defects

Defects in the central visual field can limit the extrafoveal vision that is critical to the task of reading. This region, referred to as the reading visual field, gives a sufficient size of perceptive span to allow further scanning of the text in an organized fashion. Defects in this region of the visual field, depending on their location and shape, lead to a variety of reading disturbances and the adaptive strategies for dealing with them (for a detailed discussion, see under "Further Reading" Trauzettel-Klosinski, Neuro-Ophthalmology 27 [1–3]: 79–90, 2002).

Central Scotoma (■ Fig. 24.2, 1 b–d)

An absolute central scotoma with central fixation results in an obscuration of the reading field (■ Fig. 24.2, 1 b). This results in a marked loss of reading ability. Many patients with this problem develop a useful adaptive mechanism, eccentric viewing, or eccentric fixation. A healthy locus of retina at the border of the scotoma becomes the new center of the visual field (■ Fig. 24.2, 1 c). As a result, the scotoma is displaced away from the locus of fixation, and with it the physiologic blind spot (the latter is not depicted in ■ Fig. 24.2). The blind spot serves as a reference point, showing the extent of displacement of the scotoma.

The lower resolving power of the eccentric retinal locus can be compensated to a degree by the use of angular magnification, i.e., enlargement of the size of printed text (24.2, 1 d). This is the basis for the effectiveness of magnifying visual aids.

Ring Scotoma (■ Fig. 24.2, 2 a, b)

With preservation of a central island of foveal function surrounded by an absolute central scotoma, the tiny area of retained vision may be too small for effective reading. The insufficient size of the reading visual field results in a marked discrepancy between the acuity measures for single optotypes on the one hand and the loss of reading ability in central fixation on the other (■ Fig. 24.2, 2 a), Reading ability is retained with enlarged type only in the event that the patient is capable of eccentric fixation (■ Fig. 24.2, 2 b).

Concentric Constriction of the Visual Field (■ Fig. 24.2, 2 c)

Here too, the central island of vision may be too small to allow for reading, although some degree of reading ability can be achieved with the use of higher contrasts and very small type sizes, allowing more of a printed sequence of letters to fall within the functioning central island of remaining vision.

Homonymous Hemianopia (■ Fig. 24.2, 3)

Hemianopic defects obscure half of the reading field (■ Fig. 24.2, 3 a). In this instance, the most important variable is the distance from the center of the field to the closest margin of the defect. In instances of macular sparing, which is the case with occipital lobe disease and sparing of the occipital pole, reading may not be significantly impaired (■ Fig. 24.2, 3 b). A small paracentral homonymous defect will cause a severe problem with reading (■ Fig. 24.2, 3 c). In the event that a homonymous defect is located on the right side, the patient will not be able to generate targeted saccades to the next group of letters. Instead, numerous small and inaccurate saccades are substituted, numerous backtracking movements are made within the same line of print, and the speed of reading is markedly slowed. Reading becomes a task that is no longer enjoyable.

In the case of a left-sided hemianopia, the patient will be able to trace along the line of print with near-normal speed, but will be unable to locate quickly the first word of the next line. This degree of impairment is much less disabling than is the case with right-sided hemianopias.

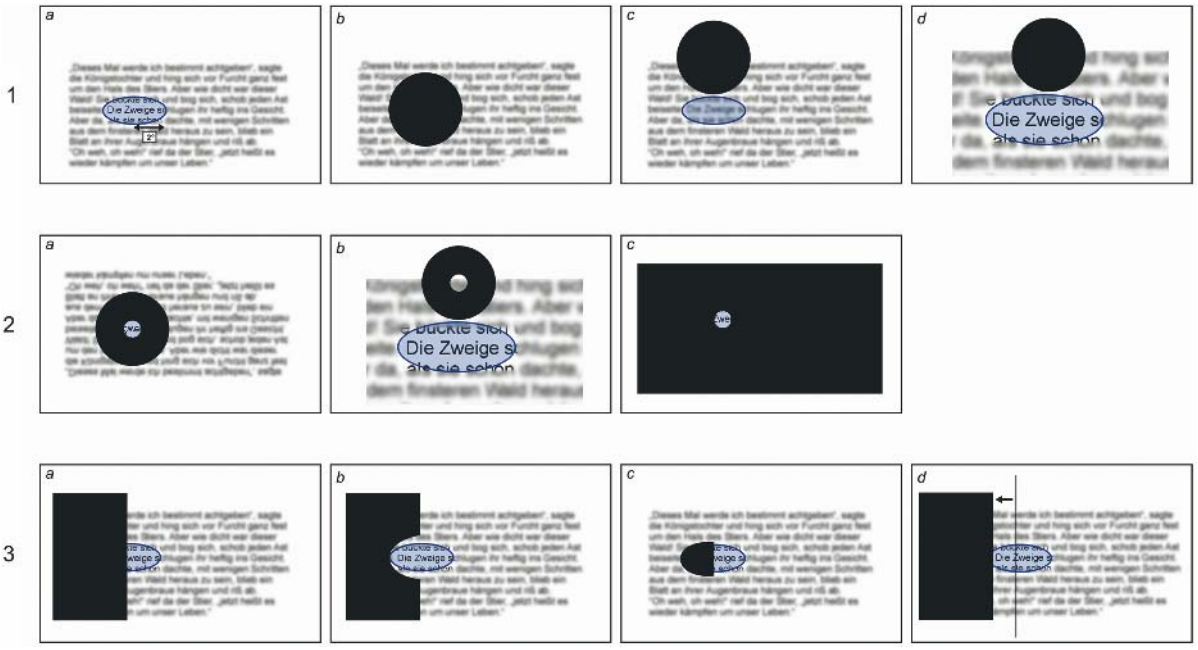


Fig. 24.2. The effect of various forms of visual field loss on the minimum reading visual field (shown in *blue*) *1a* Normal state. *1b–d* Absolute central scotoma. With central fixation the reading visual field is useless (*1b*), with eccentric fixation the central scotoma is displaced peripherally, and the eccentric locus of fixation has a lower spatial resolution (*1c*). With magnification of text, reading ability can be restored (*1d*). *2a and b* Ring scotoma. The central island is too small to be useful for reading (*2a*). Reading will require both eccentric fixation and text magnification (*2b*). *2c* Concentric constriction of the visual field. The central island of vision is too small to permit reading. *3a–d* Hemianopic loss of visual field. Without macular sparing the reading visual field is half-destroyed (*3a*); with macular sparing of adequate size the reading visual field may be unimpaired (*3b*). A small paracentral homonymous defect in the visual field can produce profound loss of reading ability (*3c*). Hemianopic visual field loss can be displaced toward the blind side by shifting fixation to an eccentric locus in the seeing half of the field, restoring a small band of perception to the hemianopic side (*3d*)

A number of adaptive strategies that can help with this class of reading problem. Despite the retention of intact foveal function, many patients without macular sparing can learn to use a form of eccentric fixation. This strategy allows the patient to displace the field defect toward the hemianopic side, allowing the intact hemifield to overlap the vertical meridian (■ Fig. 24.2, 3 d). Thus, they sacrifice some of their acuity in favor of a small area of perception that has been shifted into the affected hemifield, allowing as much as 1 to 1.5 ° of overlap. For the task of reading, this is a very significant improvement. This ability is thought to be the result of a form of functional plasticity of cortical processing, an acquired skill that requires much practice to master.

Another adaptive strategy is the learning of predictive saccades, in which the foveal fixation point is jumped toward the blind side by estimating the distance to the next line of print (in left hemianopias) or the next group of letters (in right hemianopias).

Another important compensating strategy for homonymous hemianopias that improves spatial orientation (though not reading) is the use of regularly initiated saccadic shifts of fixation toward the blind side. This strategy, just like that of eccentric fixation, shifts the blind portions of the visual field toward the hemianopic side and can lead to a faulty interpretation of conventional perimetric results as indicating preservation or recovery of some vision on the hemianopic side.

Heteronymous hemianopias, as in chiasmal disease, can cause problems with reading that are a result of the hemifield slide phenomenon (see Chaps. 2 and 15).

Rehabilitation

The goal of rehabilitation is to regain and optimize the reading ability. To assess the residual function as a basis for rehabilitation, a standardized low vision test battery can be used (see Hahn et al. 2006, under “Further Reading” and

Table 24.1. The effect of visual field defects on reading ability

Foveal function →	Fixation →	Problem	← Solution
Extinguished	Eccentric	Low retinal resolution	Magnification
Intact	Central	Reduced size of reading visual field	Training in the use of eccentric fixation
Reduced	Central	Combination of poor resolution and small visual field	Contrast enhancement

www.amd-read.net). The most effective measures include visual aids (magnification and contrast enhancement) as well as training in the proper use of visual aids, establishing an optimal (i.e., eccentric) fixation locus, and specific training for the improvement of reading. For hemianopias, magnification is generally not helpful. Instead, tactile clues (ruler, cylindric ruler with a red guide line, or index finger), rotation of reading material by 90° to read in an up or down direction, and/or special training are more likely to be of help. The success rate for the use of visual aids is fortunately quite good: 90% for patients treated at the Low Vision Clinic in the University Eye Hospital Tübingen. Attempts at rehabilitation, even in the worst instances of visual loss, are always worth trying.

Conclusion

The prerequisites for retention or recovery of reading ability in patients with visual field defects are summarized in ■ Table 24.1:

- If foveal function has been destroyed and fixation is eccentric, the problem is one of inadequate retinal resolution. This type of problem can often be helped with magnification of reading material.
- If foveal function is intact and fixation is central, the size of the reading visual field is the problem. Restoration of reading ability requires development of or training in the use of eccentric fixation.
- If foveal function is reduced and fixation remains central, a composite deficit partly of poor resolution and partly of small size of the reading visual field occurs. In this situation, an increase in the contrast of reading material is often helpful.

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