mechanisms of clinical signs

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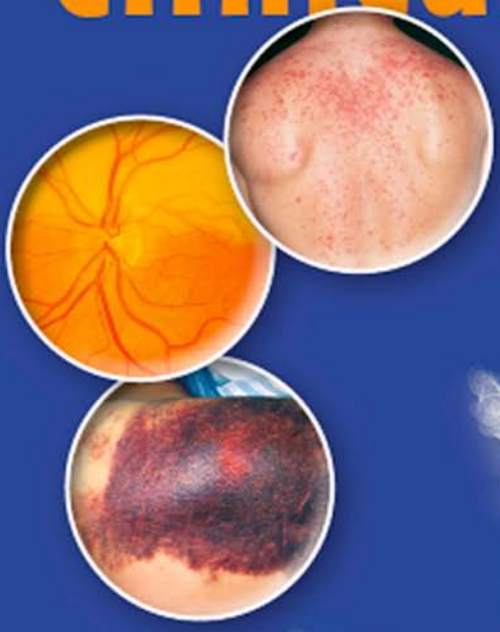

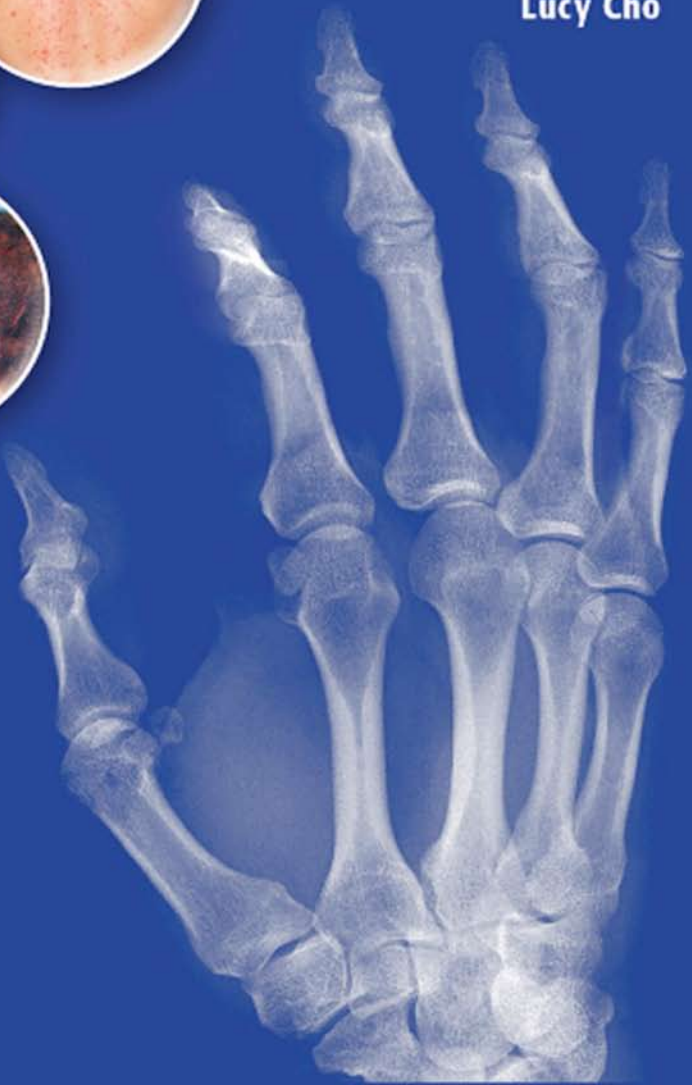

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Contents

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Foreword

In the vast world of medical textbooks and literature, rarely does a book emerge that is truly unique in its educational content and approach. While endless books are available about clinical signs in the practice of medicine, and specifically in the diagnosis of human disease, few describe the pathophysiological mechanisms underpinning these clinical signs, i.e. why these clinical signs arise and what they mean. *Mechanisms of Clinical Signs* is a wonderful, comprehensive, easy-to-read reference book that describes clinical signs spanning all aspects of medicine and surgery. The book is clearly set out so that reference to specific systems and signs is very easy to follow. There is a uniform set of subheadings for each sign – Description, Condition/s associated with, Mechanism/s and Sign value – adding to the ease with which the book is read. The explanations for the mechanisms underlying each sign are brief but accurate and informative, and provide sufficient information for the reader to understand the mechanism as well as directions for further reading if the reader chooses to do so.

This textbook is likely to be of value to medical trainees at all levels, from medical students entering their first clinical rounds on the wards to trainees about to embark on their basic physician training. I congratulate the authors, who had the insight as medical students to recognise a gap in our understanding of clinical signs. They have developed a wonderful resource that will not only educate our future doctors, but also facilitate the translation of this knowledge to the improved diagnosis and treatment of our patients.

Professor Chris Semsarian

Preface

Throughout our medical training, we are always learning how to look, listen and feel. These skills allow us to elicit critical signs that help narrow the differential diagnoses and identify the disease process causing our patient's illness. This allows us to narrow the field when initiating investigations into the cause – be it a virus or gene, trauma, immunological insult etc.

This book is not designed to show you how to elicit these signs. There are a number of texts, most notably Talley and O'Connor's *Clinical Examination* and the similarly named Macleod's, which can guide the novice through the many and varied system examinations. Nor will it explain the disease process in minute pathological detail as, again, there is a plethora of medical references available for that purpose.

The focus of this text is on the mechanism underlying the clinical sign – or why particular signs occur and what they mean. Most medical students and junior doctors can recall numerous occasions when they have been asked why clubbing occurs, what the mechanism of peripheral oedema is in hepatic failure, or similar questions that often lead to a stunned silence in front of their favourite (or least favourite) professor. This book will not only help you prepare for the Q and A session most consultants love to spring on students and junior doctors, it will also help you study for practical examinations such as OSCEs and long cases. In short, if you can explain the mechanism, you know not just the sign but its significance as well. This knowledge will serve you in good stead not only as a student or junior but in your own capacity as educator. The most common questions you will hear from patients and their families are 'What causes that?' and 'What does it mean?' The ability to provide answers simply and without jargon will go a long way towards creating an impression of you as an able practitioner.

Clearly, there is an almost infinite number of clinical signs in medicine and there is limited yield in knowing each and every one of them. Consequently, some of the more esoteric signs have not been included here unless we thought they would provide specific value to the reader. Our focus is explaining classic signs that you may encounter every day and helping you to understand what they mean.

In a world of evidence-based medicine, it is important to understand the value of the clinical sign with regard to both its presence and absence. Does it even matter if a sign is present or not? In writing this textbook, we have been surprised by both the value and lack of value of a number of signs used every day in the diagnostic process. Small sections on evidence, whether it is strong or poor, have been included for as many signs as possible to help the reader.

The text has been designed to work as an easy reference guide. As such, chapters are organised by body system and signs are generally listed in alphabetical order. When one sign crosses multiple body systems, easy reference between chapters has been provided. We have also included a table of contents by condition or disease, which enables the reader to easily reference all the signs that relate to a particular condition, for example, Cushing's syndrome. Wherever possible, illustrations and simplified flow diagrams have been used to assist explanation. If the mechanism of a sign is not a proven fact, the most current theories have been summarised. Where no such theory exists, the mechanism has been referred to as unknown and perhaps will stimulate the reader to do their own research.

There is one unique feature in the 'Neurological signs' chapter. In writing this expansive chapter, it became apparent that, to understand the mechanisms of neurological signs, an understanding of the anatomical pathways involved is key. In order to simplify matters, we have added a 'topographical anatomy' section, which identifies the relevant neuroanatomy with regard to that sign.

We hope you find this textbook not only enhances your understanding of clinical signs and their causes, but also furthers your ability to communicate that knowledge to your patients, peers and seniors.

All the best,
Mark Dennis
William Talbot Bowen
Lucy Cho

CAVEAT:

While researching this book, the authors used reference texts as well as Medline, PubMed, Embase, SCIRUS and other databases – firstly to identify all relevant signs and secondly to find the most up-to-date information about them. Every attempt has been made to provide the reader with the most recent information; however, with knowledge in medicine expanding at an exponential rate, it is possible that current thinking regarding causes may have been superseded by the time of publication.

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Abbreviations

5-HT	5-hydroxytryptamine (serotonin)
AC	acromioclavicular
ACA	anterior cerebral artery
ACE	angiotensin-converting enzyme
ACL	anterior cruciate ligament
ACTH	adrenocorticotropic hormone
ADP	adenosine diphosphate
ADH	antidiuretic hormone (vasopressin)
AIDS	acquired immune deficiency syndrome
AION	anterior ischaemic optic neuropathy
AN	acanthosis nigricans
ANR	atrial natriuretic response
ANS	autonomic nervous system
AP	anteroposterior
AR	aortic regurgitation
ARDS	acute respiratory distress syndrome
ASD	atrial septal defect
AV	arteriovenous
AV (node)	atrioventricular (node)
AVM	arteriovenous malformation
BMI	body mass index
BP	blood pressure
BPH	benign prostatic hypertrophy
BPPV	benign paroxysmal positional vertigo
cAMP	cyclic adenosine monophosphate
CCK	cholecystokinin
CG	ciliary ganglion
CGL	chronic granulocytic leukaemia
CGRP	calcitonin gene-related peptide
CHF	congestive heart failure
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CMC	carpometacarpal
CML	chronic myeloid leukaemia
cMOAT	canalicular multispecific organic anion transporter
CMT	Charcot–Marie–Tooth (disease)
CMV	cytomegalovirus
CN	cranial nerve
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COX	cyclo-oxygenase
CRAO	central retinal artery occlusion
CREST	calcinosis cutis, Raynaud's phenomenon, (o)esophageal dysfunction, sclerodactyly, telangiectasia syndrome
CRH	corticotrophin-releasing hormone
CRVO	central retinal vein occlusion
CS	cavernous sinus
CSA	central sleep apnoea
CSF	cerebrospinal fluid
CT	computerised tomography
CV	cortical veins
CVP	central venous pressure
DAS	dorsal acoustic stria
DHEA-S	dehydroepiandrosterone sulfate
DI	diabetes insipidus
DIP	distal interphalangeal
DM	diabetes mellitus
DRE	digital rectal examination
DVT	deep vein thrombosis
EBV	Epstein–Barr virus
EGFR	epidermal growth factor receptor
EMH	extramedullary haematopoiesis
ENAC	epithelial sodium (Na) channel
EOM	extraocular muscle
EW	Edinger–Westphal nucleus
FA	femoral artery
FABER	flexion abduction external rotation
FGFR	fibroblast growth factor receptor
FSH	follicle-stimulating hormone
G6PD	glucose-6-phosphate dehydrogenase
GABA	gamma-aminobutyric acid
GAS	group A streptococcus
GBS	Guillain–Barré syndrome
GH	growth hormone
GI	gastrointestinal
GnRH	gonadotrophin-releasing hormone
GORD	gastro-oesophageal reflux disease
GP	glycoprotein
GPe	globus pallidus pars externa
GPi	globus pallidus pars interna

Gs	guanine nucleotide-binding protein that couples to TSH receptor
GV	great vein of Galen
Hb	haemoglobin
HbSC	sickle cell haemoglobin C
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HOCM	hypertrophic obstructive cardiomyopathy
HPOA	hypertrophic pulmonary osteoarthropathy
HPV	human papilloma virus
HSV	herpes simplex virus
IAS	intermediate acoustic stria
IBD	inflammatory bowel disease
ICA	internal carotid artery
ICP	intracranial pressure
ICV	internal cerebral vein
IFN	interferon
IGF-1	insulin-like growth factor-1
IJ	internal jugular vein
IL	interleukin
INC	interstitial nucleus of Cajal
INO	internuclear ophthalmoplegia
IO	inferior oblique (muscle or subnucleus)
IR	inferior rectus (muscle or subnucleus)
ISS	inferior sagittal sinus
IVC	inferior vena cava
JVP	jugular venous pressure
LA	left atrial
LBBB	left bundle branch block
LBT	long head of biceps tendon
LGN	lateral geniculate nucleus
LH	luteinising hormone
LPS	lipopolysaccharides
LR	lateral rectus (muscle)
LR	likelihood ratio
LR	livedo reticularis
LS	lateral sinus
LTB_4	leukotriene B_4
LV	left ventricular
MAOI	monoamine oxidase inhibitor
MCA	middle cerebral artery
MCP	metacarpophalangeal
MD	muscular dystrophy
MDMA	methylenedioxymetham phetamine (ecstasy)
MDPK	myotonic dystrophy protein kinase
MEN	multiple endocrine neoplasia
MLF	medial longitudinal fasciculus
MMP	matrix metalloproteinase
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (toxicity)
MR	medial rectus (muscle)
MRF	midbrain reticular formation
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSH	melanocyte-stimulating hormone
MTP	metatarsophalangeal
MV	mitral valve
NAA	N-acetyl-L-aspartate
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NHL	non-Hodgkin lymphoma
NLD	necrobiosis lipoidica diabeticorum
NLR	negative likelihood ratio
NO	nitric oxide
NPV	negative predictive value
OCP	oral contraceptive pill
OS	opening snap
OSA	obstructive sleep apnoea
PAI-1	plasminogen activator inhibitor-1
PASP	pulmonary artery systolic pressure
PC	posterior commissure
PCA	posterior cerebral artery
PComm	posterior communicating artery
PCOS	polycystic ovarian syndrome
PCP	phencyclidine (toxicity)
PCWP	pulmonary capillary wedge pressure
PDA	patent ductus arteriosus
PDGF	platelet-derived growth factor
PFO	patent foramen ovale
PGE	prostaglandin E
PGH	prostaglandin H
PGI_2	prostaglandin I_2
PICA	posterior inferior cerebellar artery
PIP	proximal interphalangeal
PLR	positive likelihood ratio
PND	paroxysmal nocturnal dyspnoea
POMC	pro-opiomelanocortin
PPRF	paramedian pontine reticular formation
PPV	positive predictive value
PR (interval)	measured from the beginning of the P wave to the beginning of the QRS complex
PR	pulmonary regurgitation
PS	petrosal sinus

PSA	prostate-specific antigen
PSP	progressive supranuclear palsy
PTH	parathyroid hormone
PTH-rp	parathyroid hormone-related protein
PTN	pretectal nucleus
RA	rheumatoid arthritis
RA	right atrial
RAA(S)	renin–angiotensin–aldosterone (system)
RANK(-L)	receptor activator of nuclear factor kappa (ligand)
RAPD	relative afferent pupillary defect
RAR	rapidly adapting receptor
RBBB	right bundle branch block
RBC	red blood cell
riMLF	rostral interstitial medial longitudinal fasciculus
RN	red nucleus
RNA	ribonucleic acid
RR	relative risk *or* risk ratio
RTA	renal tubule acidosis
RV	right ventricular
SA (node)	sinoatrial (node)
SC	superior colliculus
SCA	superior cerebellar arteries
SCC	squamous cell carcinoma
SCFE	slipped capital femoral epiphysis
SLAP	superior labrum anterior posterior
SLE	systemic lupus erythematosus
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
SO	superior oblique (muscle)
SPS	stiff-person syndrome
SR	superior rectus (muscle or subnucleus)
SS	sigmoid sinus
SS	straight sinus
SSRI	selective serotonin reuptake inhibitor
SSS	superior sagittal sinus
STN	subthalamic nucleus
SVC	superior vena cava
T_3	triiodothyronine (thyroid hormone)
T_4	thyroxine (thyroid hormone)
TA	tricuspid annulus
TB	tuberculosis
TF	tissue factor
TGF-β	transforming growth factor-beta
TH	torcular Herophili
Th-1	helper T cell type 1
TIA	transient ischaemic attack
TNF	tumour necrosis factor
TPA	tissue plasminagen activator
TRH	thyrotrophin-releasing hormone
TS	transverse sinus
TSH	thyroid-stimulating hormone
TSHR	thyroid-stimulating hormone receptor
TTP	thrombotic thrombocytopenic purpura
TXA	thromboxane
URTI	upper respiratory tract infection
V2 (receptor)	arginine vasopressin receptor 2
VAS	ventral acoustic stria
VEGF	vascular endothelial growth factor
VIP	vasoactive intestinal peptide
VL	ventral lateral
VSD	ventricular septal defect
vWF	von Willebrand factor
VZV	varicella zoster virus

CHAPTER 1

Musculoskeletal Signs

Anterior drawer test

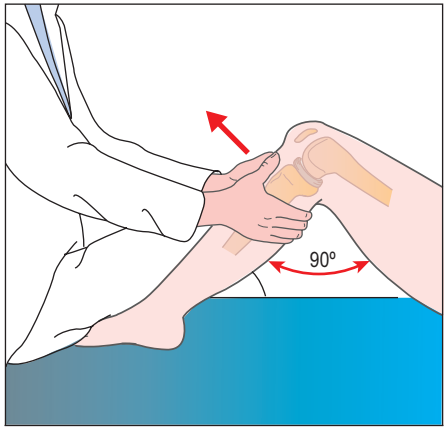

FIGURE 1.1 Anterior drawer test for anterior cruciate ligament deficiency

DESCRIPTION

On grasping the leg in the upper one-third of the tibia and pulling it anteriorly, there is noticeable laxity and movement of the tibia forward on the femur.

CONDITION/S ASSOCIATED WITH

- Anterior cruciate ligament (ACL) injury/tear

MECHANISM/S

The ACL acts as the primary restraint on forward movement of the tibia on the femur, so when torn the restriction is released and the tibia is able to move further anteriorly.

SIGN VALUE

The anterior drawer test is a questionable test for ACL injuries.

There have been wide variances in the results of available research. In one review the sensitivity of the sign was 27–88%; however, the specificity only ranged from 91–99% and the positive LR was 11.5,[1] making it valuable if present. In another meta-analysis,[2] the positive LR was 3.8 and the sensitivity was 9–93% and the specificity was 23–100%; however, this study included small trials that may have skewed the results.

On balance, it appears a relatively specific but not sensitive test.

Apley's grind test

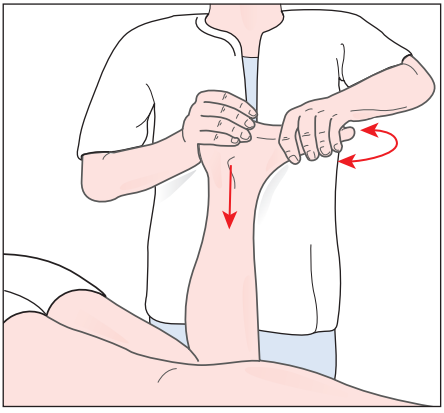

FIGURE 1.2 Apley's grind test

DESCRIPTION

With the patient lying on the stomach and the knee flexed to 90°, downward pressure is applied to the heel, compressing the tibia onto the femur. The examiner then internally and externally rotates the tibia on the femur. If this produces pain, the test is considered positive.

CONDITION/S ASSOCIATED WITH

- Meniscal injury

MECHANISM/S

Direct pressure from the tibia towards the femur is aimed at 'catching' or hitting the damaged meniscus. If damage is present, pain will be elicited.

SIGN VALUE

A few heterogeneous studies have been completed. A systematic review of seven of these studies found a pooled sensitivity of 60.7% and specificity of 70.2% with an odds ratio of 3.4,[3] making Apley's test not a particularly useful diagnostic test of meniscal injury. These findings were borne out in another meta-analysis.[4] In addition, many practitioners no longer perform Apley's grind test as the pain produced can be excruciating if an injury is present.

Apley's scratch test

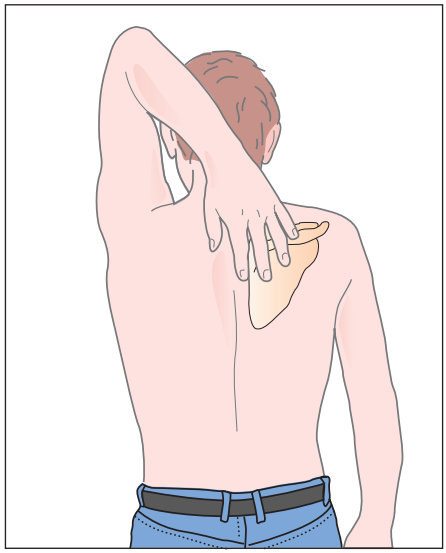

FIGURE 1.3 Apley's scratch test

Based on Woodward T, Best TM, Am Fam Phys 2000; 61(10): 3079–3088.

DESCRIPTION

Performed by asking the patient to reach and 'scratch' at the opposite scapula, both from above and below. Pain, limitation or asymmetry on performing these movements can be considered 'positive'.

CONDITION/S ASSOCIATED WITH

Common

Many types of shoulder joint injuries will produce pain on Apley's scratch test.

- Rotator cuff tear/tendonitis
- Sub-deltoid bursitis
- Acromioclavicular joint sprain

MECHANISM/S

The global range of movement and, more specifically, abduction/adduction and internal/external rotation of the shoulder joint are examined by this test. Although thought to elicit rotator cuff pathology, in particular supraspinatus injury, almost any capsular, ligamentous, muscle or bony injury to the shoulder joint may cause a positive test.

SIGN VALUE

Apley's scratch test is a good test of overall function of the shoulder joint; however, it is not specific to a particular part of the anatomy and is more a general screen of range of motion.

Apparent leg length inequality (functional leg length)

1

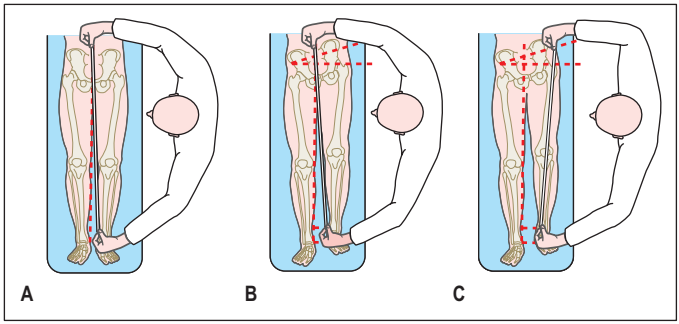

FIGURE 1.4 Measurement of leg lengths

A The apparent leg length is the distance from the umbilicus to the medial malleolus. **B** Pelvic obliquity causing an apparent leg-length discrepancy. **C** The true leg length is the distance from the anterior superior iliac spine to the medial malleolus.

Based on Firestein GS, Budd RC, Harris ED et al, *Kelley's Textbook of Rheumatology*, 8th edn, Philadelphia: WB Saunders, 2008: Fig 42-24.

DESCRIPTION

When measuring from the umbilicus to the medial malleolus of each leg, there is disparity between the two limbs. Technically described as unilateral asymmetry of the lower extremities without any concomitant shortening of the osseous (bony) components of the lower limb.

CONDITION/S ASSOCIATED WITH

- Altered foot mechanics
- Adaptive shortening of soft tissues
- Joint contractures
- Ligament laxity
- Axial mal-alignments

MECHANISM/S

An apparent or functional leg length inequality may occur at any point from the ileum to the inferior-most aspect of the foot[5] for a number of reasons.

Ligament laxity

In this situation, the bones are the same length; however, the ligaments on one side (e.g. in the hip joint) may be more flexible or longer than their counterparts on the other side, making the femur sit lower in the joint capsule and appear longer on measurement.

Joint contracture

Joint contractures create stiffness and do not allow a full range of movement. If the knee joint is contracted in a flexed position, the affected side will not be as long as the opposite side even if in a fully extended position.

Altered foot mechanics

Excessive pronation of the foot eventuates in and/or may be accompanied by a decreased arch height compared to the 'normal' foot, resulting in a functionally shorter limb.[5]

SIGN VALUE

As in *true leg length inequality,* considerable variation in what is thought to be a clinically significant discrepancy and accuracy in clinical measurement has been reported.[5] It therefore has limited value as a diagnostic or prognostic test. If there is significant variation in leg length (>2 cm) coupled with clinical signs, further investigation is warranted.

Apprehension test (crank test)

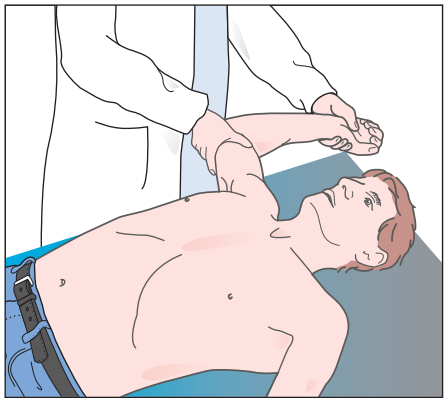

FIGURE 1.5 Apprehension test

The arm is abducted and in an externally rotated position. Note the right arm of the examiner is providing anterior traction on the humerus, pulling the posterior part of the humeral head forward. The same test can be done from the back, with the patient sitting up and the examiner pushing forward on the posterior head of the humerus.

DESCRIPTION

The apprehension test tries to determine whether glenohumeral joint instability is present. With the patient sitting or supine, the shoulder is moved passively into a fully abducted and externally rotated position. *Forward* pressure is then applied to the *posterior* part of the humeral head[6] (see Figure 1.5). The test is positive if the patient feels *apprehension* that the shoulder may dislocate. It is NOT positive if it produces only pain.

CONDITION/S ASSOCIATED WITH

More common – traumatic

- Humeral head subluxation or dislocation
- Rotator cuff damage
- Anterior rim damage
- Detachment of the joint capsule from ligaments

Less common – atraumatic

- Ehlers–Danlos syndrome
- Marfan's syndrome
- Congenital absence of glenoid
- Deformities of the joint or proximal humerus

MECHANISM/S

The primary cause of a positive apprehension test is damage or dysfunction of the capsule, labrum, ligaments or muscles that maintain stability in the shoulder joint. Anterior subluxation/dislocation occurs in 95% of dislocations.

Normal people have a certain degree of shoulder joint laxity or instability, which allows for the wide array of movements possible. Key to maintaining the stability of the shoulder joint are:

- capsuloligamentous or glenohumeral ligaments – primary stabilisation
- rotator cuff muscles – subscapularis is the most important for stability
- glenoid fossa and glenoid labrum.

Disruption of any of these structures predisposes the patient to a positive apprehension test and anterior joint instability.

In the apprehension test, external rotation 'levers' the glenoid head anteriorly and is assisted by the examiner pushing the head of the humerus *forward*. If there are any (or multiple) defects in the joint stabilisers, the head of the humerus will displace anteriorly – potentially even out of the joint socket. This causes discomfort and 'apprehension' of impending dislocation.

SIGN VALUE

A reasonable test for glenohumeral joint instability, with very good specificity but only moderate sensitivity.

Initially reported by Rowe[7] as having 100% specificity for anterior joint instability. A subsequent study of 46 patients found only modest sensitivity of 52.78% but good specificity of 98.91%.[8]

Specificity is improved even further when the test is combined with other tests including the 'apprehension–relocation' test (see 'Apprehension–relocation test' in this chapter).

Apprehension–relocation test (Fowler's sign)

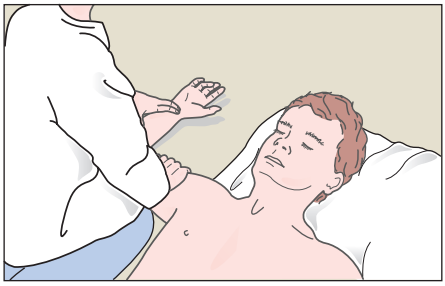

FIGURE 1.6 Apprehension–relocation (Fowler) test
Note that pressure is applied anteriorly to the proximal humerus.

DESCRIPTION

Most often used in conjunction with (and immediately after the completion of) the apprehension (crank) test (see 'Apprehension test' in this chapter). While either sitting or supine, the arm is passively moved into an abducted and externally rotated position. However, in this test the examiner's right hand is on the *anterior* aspect of the proximal humerus and is used to push the head of the humerus *backwards* (posteriorly). The test is said to be positive if the patient gets relief from symptoms produced by the apprehension test. In short, if the examiner can elicit apprehension from forward movement that is relieved by backwards motion in the same plane, the test is positive.

CONDITION/S ASSOCIATED WITH

- Anterior joint instability – see disorders under 'Apprehension test'

MECHANISM/S

The underlying anatomy and causes of anterior joint instability are outlined under 'Apprehension test' and apply equally here.

The main difference between the two tests is the symptomatic relief given by posterior pressure applied to the proximal humerus. This is thought to be caused by either of the following scenarios:

1. The humeral head, which is on the cusp of subluxation anteriorly, is pushed backwards and therefore reduced to its normal anatomical location.
2. The posterior pressure applied acts as a 'support structure' to the shoulder joint, giving the patient more confidence that subluxation will not occur and therefore relieving apprehension.[9]

SIGN VALUE

The relocation test is considered by some[10] to be the gold standard test of anterior instability. When relief of *apprehension and NOT pain* is used as the indicator for a positive test, it has excellent specificity and PPV.

Studies completed by Speer et al[11] and Lo et al[8] found it to be a very specific test in diagnosing anterior instability with sensitivity of 68%, specificity of 100% and PPV of 100% and sensitivity of 31.94%, specificity of 100% and PPV of 100% in their respective studies.

However, when using *pain or apprehension* as an indicator of the test, Lo et al[8] found less specific results with sensitivity of 45.83%, specificity of 54.36% and PPV of 56.26%.

In summary, if relief of apprehension is present in completing the apprehension–relocation test, anterior instability of the shoulder joint is almost certain to be present. Its usefulness is further increased if used in conjunction with the apprehension test.

Bouchard's and Heberden's nodes

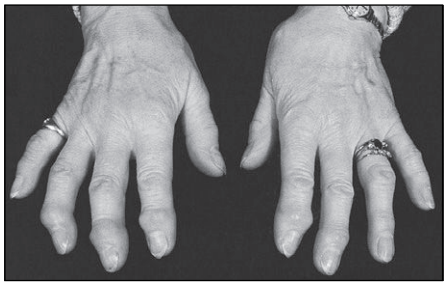

FIGURE 1.7 Prominent Heberden's nodes

Based on Ferri FF, *Ferri's Clinical Advisor*, Philadelphia: Elsevier, 2011: Fig 1-223.

DESCRIPTION

Bouchard's nodes are bony outgrowths or nodules found over the *proximal* interphalangeal joints of the hands.

Heberden's nodes are located over the *distal* interphalangeal nodes.

CONDITION/S ASSOCIATED WITH

- Osteoarthritis
- Familial

MECHANISM/S

The mechanism is unclear.

A number of studies have implicated *bony osteophyte growth* as the principle cause of Heberden's and Bouchard's nodes.[12] Other contributing factors or theories include:

- genetic predisposition
- endochrondral ossification of hypertrophied cartilage as a result of chronic changes from the osteoarthritis process[13]
- traction spurs growing in tendons in response to excessive tension, repetitive strain or contracture.[12]

SIGN VALUE

The presence of Bouchard's or Heberden's nodes is a valuable sign with evidence that they are a strong marker for interphalangeal osteoarthritis[14,15] and possibly a predisposition to generalised osteoarthritis.[16,17] There is evidence that there is a correlation between the presence of these nodes and actual radiographic changes of osteoarthritis.[18]

Boutonnière deformity

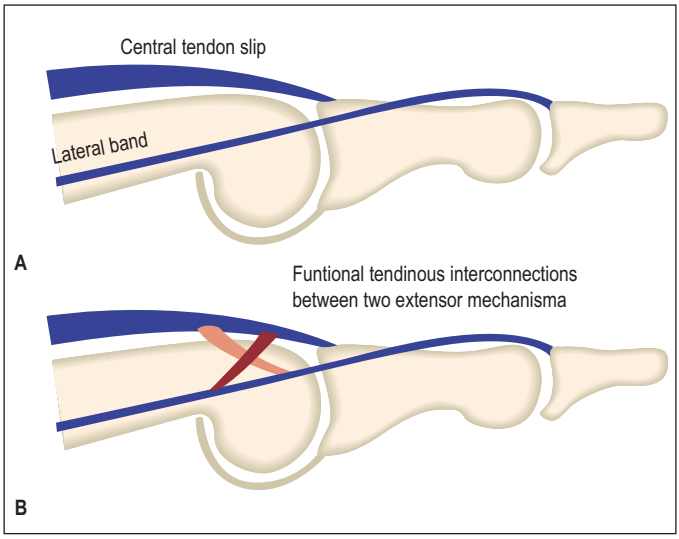

FIGURE 1.8 Digital extensor mechanism

A The proximal interphalangeal joint is extended by the central tendon slip (an extension of the hand's dorsal extensor tendon). **B** The *X* is a functional representation of the fibrous interconnections between the two systems.

Based on DeLee JC, Drez D, Miller MD, *DeLee and Drez's Orthopaedic Sports Medicine*, 3rd edn, Philadelphia: Saunders, 2009: Fig 20B2-27.

DESCRIPTION

Used to describe a deformity of the finger in which the proximal interphalangeal (PIP) joint is permanently flexed towards the palm, while the distal interphalangeal (DIP) joint is bent away from the palm.

CONDITION/S ASSOCIATED WITH

- Traumatic injuries
- Lacerations
- Infections
- Inflammatory conditions

MECHANISM/S

Central to the mechanism is disruption or avulsion of the *central tendon slip*. In fact, this sign derives its name from the appearance of the central tendon slip, which was thought to resemble a button hole (*boutonnière* in French) when torn.

The central tendon slip attaches to the base of the middle finger and its main job is to extend it specifically at the PIP joint with assistance of some other bands and tendons.

If the central tendon is disrupted or avulsed (pulled off the base of the middle phalanx), the actions of the flexor tendons (pulling the phalanx towards the palm) will be unopposed.

The DIP joint is hyperextended as the central tendon slip elastically retracts and pulls back on the lateral bands.

Trauma

Forced flexion of an extended PIP joint may cause detachment of the central tendon slip. In addition, crush injuries or any other trauma that damages the central tendon slip can cause a boutonnière deformity.

Laceration

Direct lacerations of the central tendon slip will cause the deformity through the above mechanism.

Infection

Infections of the joint and/or skin can lead to inflammation and disruption of the central tendon slip.

Inflammatory

Pannus in the PIP joint (such as is seen in rheumatoid arthritis) may invade the central slip tendon and disrupt it and, therefore, lead to the characteristic changes.[19]

Alternatively, chronic inflammation and synovitis of the joint can push it into flexion, elongating the central slip tendon and ultimately leading to rupture. As a

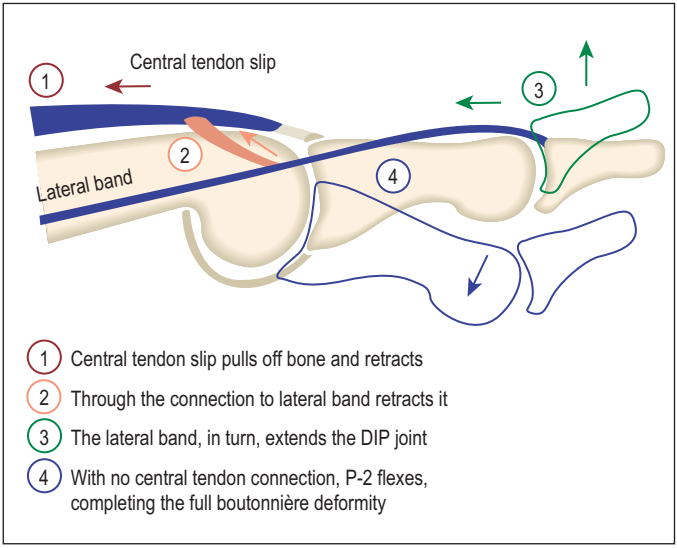

FIGURE 1.9
Pathoanatomy of boutonnière deformity

The sequence is: rupture of the central tendon slip, which then simultaneously pulls on the lateral bands, pulling the DIP joint into extension as the middle phalanx, without central slip connection, collapses into some flexion.

Based on DeLee JC, Drez D, Miller MD, *DeLee and Drez's Orthopaedic Sports Medicine*, 3rd edn, Philadelphia: Saunders, 2009: Fig 20B2-28.

result of this, the lateral bands proximal to the PIP joint are displaced. This places increased tension on the DIP joint extensor mechanism, leading to hyperextension and limited flexion of the DIP joint.[20–23]

SIGN VALUE

Boutonnière deformity is by no means specific, although it is obviously always pathological. It is said to occur in up to 50% of patients with rheumatoid arthritis

Bulge/wipe/stroke test

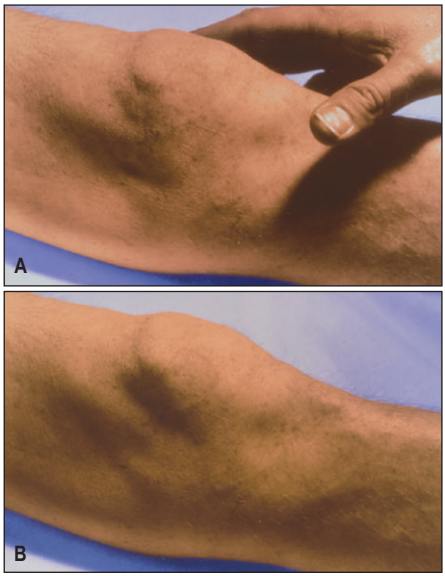

FIGURE 1.10 Demonstration of the bulge sign for a small synovial knee effusion

The medial aspect of the knee has been stroked to move the synovial fluid from this area (shaded depressed area in **A**). **B** shows a bulge in the previously depressed area after the lateral aspect of the knee has been tapped.

Based on Firestein GS, Budd RC, Harris ED et al, *Kelley's Textbook of Rheumatology*, 8th edn, Philadelphia: WB Saunders, 2008: Figs 35-9A and B.

DESCRIPTION

The bulge, wipe or stroke test is used to look for effusion in the knee joint. The patient lies flat and the examiner strokes upwards with the edge of the hand on the medial side of the knee to 'milk' fluid into the lateral compartment, and continues pushing this fluid downwards on the lateral side. The test is positive if the examiner can see a wave of fluid heading back towards the medial side of the knee.

CONDITION/S ASSOCIATED WITH

Any condition causing a knee effusion, including:

More common

- Osteoarthritis and overuse syndrome
- Trauma
- Arthritic disorders
- Infection
- Gout

Less common

- Pseudogout (calcium pyrophosphate deposition disease)
- Tumour

MECHANISM/S

The mechanism causing this sign is simple mechanical manipulation of a swelling or effusion of the knee.

Knee effusions may arise from trauma, overuse or systemic disease but, regardless of aetiology, occur due to inflammation in and around the joint space. The wipe or bulge test is simply attempting to corral the effusion into one area and move it around, making it easier to see and quantify what may otherwise be spread over and around the knee joint.

SIGN VALUE

Limited evidence has been gathered on the value of this test as an individual sign. It has been suggested[24] that this test may pick up on *as little as 4–8 mL of swelling* and be more sensitive in identifying small effusions than the patellar tap.

One small study[25] showed a low sensitivity of 11–33% and higher specificity of 66–92% (depending on examiner) for identifying the presence of a knee effusion. This study showed the wipe test to be more specific than the patellar tap.

The presence of an effusion has been reviewed with other signs in regard to diagnosis of fractures and osteoarthritis. An effusion in the absence of acute traumatic injury or systemic disease *is* a reliable indicator of osteoarthritis.[26] However, in the identification of a clinically significant knee fracture, a joint effusion only has moderate utility with a sensitivity of 54–79% and specificity of only 71–81%.[1]

Butterfly rash (malar rash)

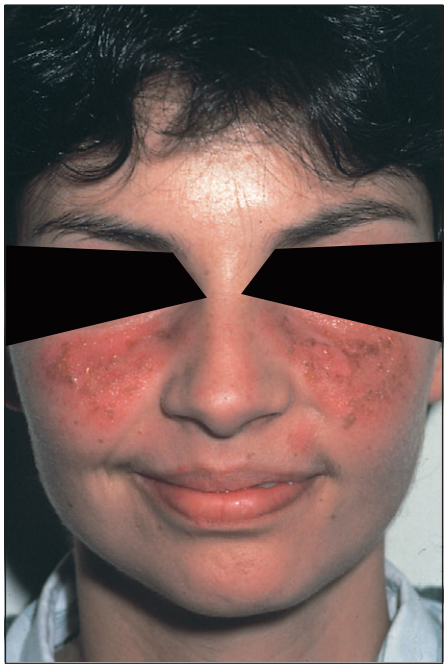

FIGURE 1.11 Malar rash of SLE

Reproduced, with permission, from Goldman L, Ausiello D, *Cecil Medicine*, 23rd edn, Philadelphia: Saunders, 2007: Fig 287-3.

DESCRIPTION

A red or purple macular, mildly scaly rash that is seen over the bridge of the nose and on both cheeks in the shape of a butterfly. The rash spares the nasolabial folds, which helps distinguish it from other rashes (e.g. rosacea). It is also photosensitive.

CONDITION/S ASSOCIATED WITH

Common

- Systemic lupus erythematosus (SLE)
- Dermatomyositis

MECHANISM/S

The exact mechanism is unclear. However, like the underlying disorder in SLE, it is thought to result from an autoimmune reaction resulting from genetic, environmental and immunological factors.

Some of the factors shown to be involved include:[27]

- A genetic predisposition to ineffective or deficient complement leading to a failure to clear immune complexes of apoptotic cells, which in turn increases the chance of the development of autoimmunity.
- Sunlight has been shown to damage and/or induce apoptosis of keratinocyte proteins in the epidermis and can stimulate autoantibody production. Sunlight may also increase the chance of keratinocytes being destroyed by complement and antibody-dependent mechanisms.
- Altered cellular and humoral immunity reactions have been seen in studies reviewing cutaneous manifestations of lupus.

It is likely that a combination of these factors leads to immune deposition in the skin, damage, oedema and the characteristic malar rash.

SIGN VALUE

The malar rash is of value in diagnosis of lupus when put into context with other signs or symptoms. It is seen in approximately 40% of patients with SLE.[27] Therefore, its absence by no means precludes a diagnosis of the disease.

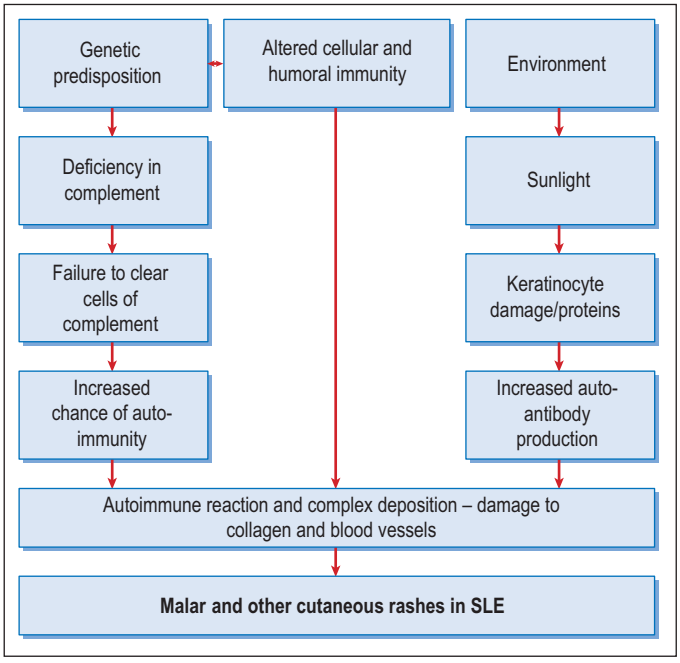

FIGURE 1.12 Mechanism of malar rash

Calcinosis/calcinosis cutis

DESCRIPTION

Calcinosis refers to the formation/deposition of calcium in soft tissue. Calcinosis cutis more specifically refers to calcium deposits found in the skin.

CONDITION/S ASSOCIATED WITH

Conditions associated with calcinosis may be classified as dystrophic, metastatic, tumour-related, iatrogenic or idiopathic.

- Dystrophic calcinosis
  - Scleroderma
  - Dermatomyositis
  - SLE
  - Systemic sclerosis
  - Burns
- Metastatic
  - Due to hypercalcaemia or hyperphosphataemia of any cause
  - Chronic renal failure – most common
  - Excess vitamin D
  - Primary hyperparathyroidism – rare
  - Paraneoplastic hypercalcaemia
  - Destructive bone disease – e.g. Paget's disease
- Iatrogenic
  - Calcium gluconate injections
  - Tumour lysis syndrome secondary to chemotherapy

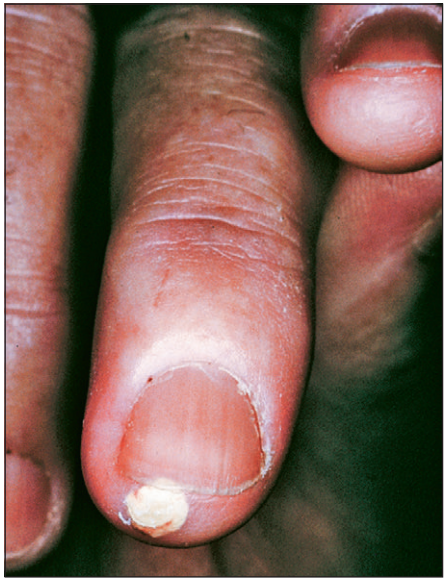

FIGURE 1.13 Calcinosis

Hard, whitish nodules on the chest representing dystrophic calcinosis in this patient with dermatomyositis.

Reproduced, with permission, from James WD, Berger T, Elston D, *Andrews' Diseases of the Skin: Clinical Dermatology*, 11th edn, Philadelphia: Saunders, 2011: Fig 26-12.

GENERAL MECHANISM/S

The mechanism is unclear in most forms of calcinosis. Calcium compound deposits (hydroxyapatite or amorphous calcium phosphate) in tissue are the common pathway to the characteristic lesions; however, how and why these are formed is not always obvious.

Dystrophic calcinosis

Dystrophic calcinosis is said to occur when *crystals of calcium phosphate or hydroxyapatite* are deposited in the skin *secondary to inflammation, tissue damage and degeneration.*[28] Calcium and phosphate levels are usually *normal*. Proposed mechanisms include:

- High local levels of alkaline phosphatase break down a pyrophosphate that normally inhibits calcification.[29]
- Tissue breakdown may lead to denatured proteins that bind to phosphate. These phosphate–protein compounds may react with calcium and thus provide a nidus for calcification.[30]

Metastatic calcinosis

The key to metastatic calcinosis is abnormal calcium or phosphate metabolism with high levels of either or both present. Excess calcium and/or phosphate allows for the formation and precipitation of calcium salts.

In chronic renal failure a number of mechanisms lead to altered phosphate and calcium metabolism:

- Decreased renal excretion of phosphate leads to hyperphosphataemia.
- Hyperphosphataemia results in a compensatory rise in parathyroid hormone (PTH) in an attempt to excrete phosphate. The rise in PTH results in an increase in phosphate absorption from the gut and also

mobilises more calcium from the bones, resulting in more calcium being available to precipitate with phosphate.
- Vitamin D deficiency owing to renal failure worsens initial hypocalcaemia and, therefore, further stimulates secondary hyperparathyroidism.

Iatrogenic

Intravenous administration of calcium or phosphate may cause local extravasation and precipitation of hydroxyapatite in surrounding tissue. Inflammation of the surrounding tissue secondary to the injection may also cause calcium release and protein release, contributing to precipitation.

Idiopathic

Occurs in the absence of tissue injury or systemic metabolic disturbance.

SIGN VALUE

There is very limited evidence on this sign and it is rarely seen in isolation. However, if identified, investigation is warranted given the numerous pathological states that cause it.

Charcot's foot

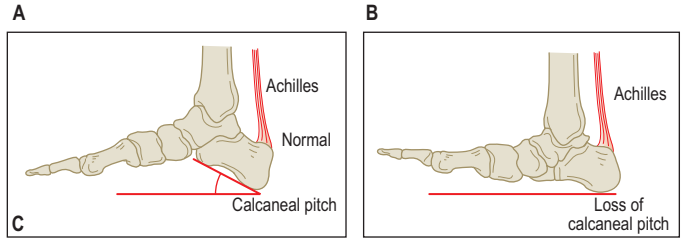

FIGURE 1.14 Charcot's foot

A, B The classic rocker-bottom Charcot foot, with collapse and then reversal of the longitudinal arch. **C** Loss of the normal calcaneal pitch, or angle relative to the floor, in patients with Charcot collapse of the arch. This leads to a mechanical disadvantage for the Achilles tendon.

Reproduced, with permission, from Mann JA, Ross SD, Chou LB, Chapter 9: Foot and ankle surgery. In: Skinner HB, *Current Diagnosis & Treatment in Orthopedics*, 4th edn, Fig 9-8. Available: http://proxy14.use.hcn.com.au/content.aspx?aID=2321540 [10 Mar 2011].

DESCRIPTION

A progressive destructive arthropathy with dislocations, pathologic fractures and destruction of the foot architecture.[31]

In its early stages, it may present to the student or clinician as a patient with unilateral foot oedema and increased temperature following a minor trauma.

In advanced disease, significant destruction of bones and joints may occur (especially in the midfoot), resulting in collapse of the plantar arch and development of 'rocker-bottom foot'.

CONDITION/S ASSOCIATED WITH

- Diabetes

MECHANISM/S

The mechanism is unclear.

Current thinking is a combination of 'neurotraumatic' theory and, more recently, the less studied 'inflammatory' theory.

In *neurotraumatic theory*, peripheral neuropathy caused by diabetes leads to a decreased pain sensation. If an acute injury occurs, whether it be a microfracture, subluxation or fracture, due to the neuropathy, the patient feels little or no pain from the damage and therefore does not 'spare' the foot when mobilising. This leads to a destructive cycle of continued loading on the injured foot and continued and worsening damage.[32]

Under the *inflammatory theory*, when the same local insult occurs (microfracture, subluxation or fracture), inflammatory

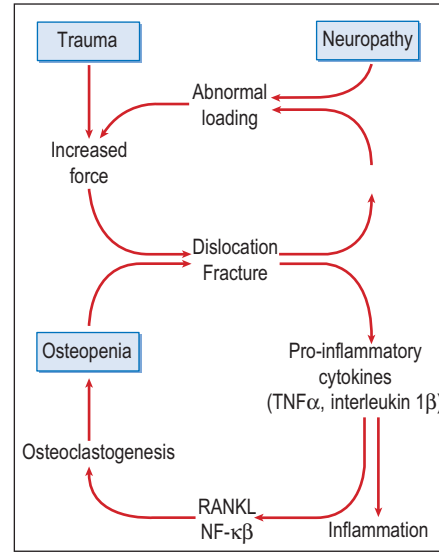

FIGURE 1.15 Inflammatory and neurotraumatic mechanisms of Charcot's foot

Based on Jeffcoate WJ, Game F, Cavanagh PR, Lancet 2005; 366: 2058–2061.

cytokines are released, including TNF-α and interleukin 1β. These two cytokines have been shown to increase activation of RANK ligand, which in turn increases the transcription factor NF-κB. The net result of this is *stimulation of the maturation of osteoclasts*, which further eat away at bone. This predisposes the patient to engage in

another vicious cycle of further fractures, inflammation, abnormal weight loading and osteolysis.[32]

Other contributing factors include:

- Sympathetic denervation in distal limbs leads to increased peripheral blood flow – hyperaemia and more inflammation.[33]
- Pre-existing osteopenia has been seen in both type 1 and type 2 diabetes via a number of mechanisms,[33] and this predisposes the diabetic patient to microfracture.
- Abnormal loading mechanics.

SIGN VALUE

The presentation itself is non-specific; however, new-onset pain, heat and swelling in a known diabetic with neuropathy is a diagnosis and sign NOT to be missed. Although less than 1% of diabetics will develop Charcot's foot, the consequences are significant with secondary ulceration affecting up to 50% of patients[34,35] and a real risk of amputation or even death as a result.[33]

Crepitus

DESCRIPTION

Grating, crunching, popping or crackling sounds able to be heard and felt over joints when moving.

CONDITION/S ASSOCIATED WITH

- Osteoarthritis
- Rheumatoid arthritis
- Any trauma to the joint being examined
- Fracture

GENERAL MECHANISM/S

Crepitus of the joints is caused when *two rough surfaces chafe or grind against* one another.

Rheumatoid/osteoarthritis

In both osteoarthritis and rheumatoid arthritis, degeneration of the articular cartilage of the joint surfaces occurs (but not by the same process – see below), causing the surfaces to become rough and/or eroded. *Two rough surfaces moving against each other* produce crepitus.

In rheumatoid arthritis, the autoimmune response with subsequent inflammation, cytokine release and pannus formation causes destruction of cartilage.

In osteoarthritis, repetitive strain with loss of glycoaminoglycans and activation of matrix metalloproteinases (MMPs) is principally responsible for damage.

SIGN VALUE

The value of crepitus as an individual sign when diagnosing osteoarthritis is limited, with a sensitivity of 89% and low specificity of 58%.[1] It is more valuable in ruling out osteoarthritis as it has a negative likelihood ratio of 0.2. When used in conjunction with other signs, including joint stiffness of more than 30 minutes, bony tenderness along joints and bony enlargement, it is more valuable as a diagnostic tool with PLR increasing to 3.1 and NLR to 0.1.[1]

Crepitus has no real place in the diagnosis of rheumatoid arthritis as other much more specific signs and symptoms are usually already present.

Dropped arm test

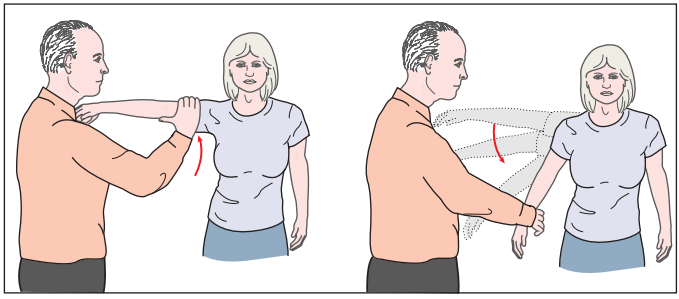

FIGURE 1.16 The dropped arm test

Based on Multimedia Group LLC, Occupation Orthopedics. Available: http://www.eorthopod.com/eorthopodV2/index.php?ID=7244790ddace6ee8ea5da6f0a57f8b45&disp_type=topic_detail&area=6&topic_id=4357b9903d317fcb3ff32f72b24cb6b6 [28 Feb 2011].

DESCRIPTION

The examiner abducts the patient's arm as far as it can go, and the patient is then asked to maintain abduction before slowly lowering the arm to neutral. A positive test occurs if the patient cannot perform or maintain the slow movement and the arm just 'drops' to the side.

CONDITION/S ASSOCIATED WITH

- Rotator cuff tear – specifically of the supraspinatus muscle
- Neurological injury

MECHANISM/S

Abduction of the arm is performed with the use of supraspinatus and deltoid muscles. The deltoid muscle is predominantly responsible for movement after approximately 15°,[36] whereas supraspinatus is responsible for the first 15° of motion. Therefore, if a rotator cuff tear is present and supraspinatus is either directly damaged or indirectly impinged, the ability of the arm to maintain abduction is impaired and the arm will drop.

SIGN VALUE

There are limited studies on the value of the dropped arm test in detecting rotator cuff tear. One small study showed a sensitivity of only 10% but a very high specificity of 98%.[37] The calculated positive likelihood ratio was greater than 10.[38] If the test is positive, it is likely a tear is present.

Finkelstein's test

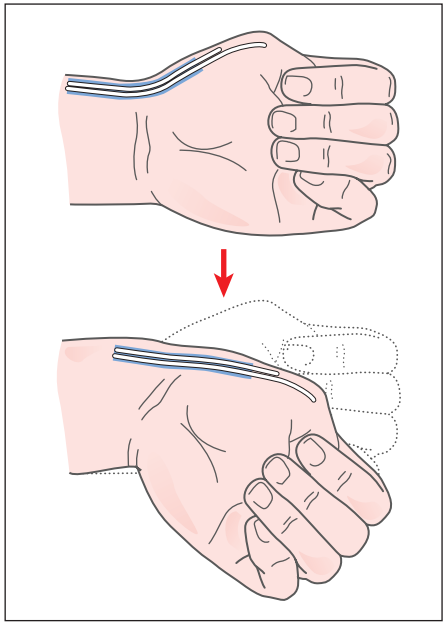

FIGURE 1.17 Finkelstein's test

With the thumb inside the hand, the wrist is ulnar-deviated. Pain indicates a positive test.

Based on Frontera WR, Silver JK, Rizzo Jr TD, *Essentials of Physical Medicine and Rehabilitation*, 2nd edn, Philadelphia: Saunders, 2008: Fig 24-2.

DESCRIPTION

Finkelstein's test is performed by the patient making a fist with the thumb inside. The hand is then quickly abducted with ulnar deviation. Pain along the radial aspect of the wrist is a positive test result.

CONDITION/S ASSOCIATED WITH

- De Quervain's tenosynovitis

MECHANISM/S

De Quervain's tenosynovitis is a term describing painful irritation of the tendons on the radial aspect of the wrist – more specifically, the abductor pollicis longus and extensor pollicis brevis and the synovial extensor compartment in which they are contained.

Repetitive trauma or inflammatory disorders cause inflammation that, in turn, causes swelling over the radial aspect of the wrist. This narrows the space through which abductor pollicis longus and extensor pollicis brevis have to pass on their way to the hand. When performing this manoeuvre the bellies of the respective muscles are moved into the narrowed compartment, irritating an already inflamed site and causing pain.[39]

Concomitant inflammation of the tendons or synovium from repetitive strain or rubbing in the inflamed extensor compartment may also contribute to the pain felt.

SIGN VALUE

There is limited research on the evidence for Finkelstein's test in diagnosing De Quervain's tenosynovitis.

Gottron's papules

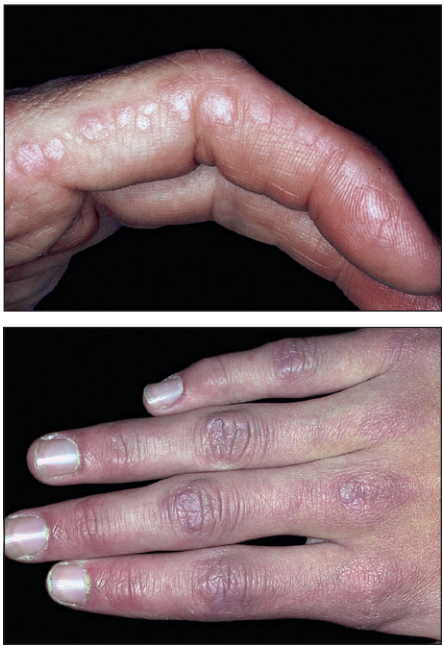

FIGURE 1.18 Gottron's papules

Found over bony prominences: fingers, elbows and knees. The lesions are slightly elevated, violaceous papules with slight scale.

Reproduced, with permission, from Habif TP, *Clinical Dermatology*, 5th edn, Philadelphia: Mosby, 2009: Figs 17-20, 17-21.

DESCRIPTION

Violaceous (violet-coloured) papules on the dorsal aspect of the interphalangeal joints.[40]

CONDITION/S ASSOCIATED WITH

- Dermatomyositis

MECHANISM/S

No clear mechanism has been identified.

A histological study[41] showed lymphocytic infiltration, epidermal atrophy and vacuoles in the basal layer of the skin in addition to other findings.

How and why the lesions occur where they do is not clear.

SIGN VALUE

Gottron's papules are said to be pathognomonic for dermatomyositis (i.e. if present, a diagnosis can be made even without muscle weakness).[42] However, there is limited evidence to support exact sensitivities and specificities.

Hawkins' impingement sign

DESCRIPTION

With the examiner standing in front of the patient, passive flexion of both the elbow and shoulder to 90° is performed, after which the examiner internally rotates the shoulder joint until pain is noted (see Figure 1.19).

CONDITION/S ASSOCIATED WITH

Most shoulder injuries including but not limited to:

- Rotator cuff injuries
- Rotator cuff tendonitis
- Subacromial spurs
- Thickened coracoclavicular ligament

MECHANISM/S

In performing this manoeuvre, the greater tuberosity of the humerus (with supraspinatus attached) is pushed into the coracoacromial ligament – producing pain.

In a healthy shoulder, the tendons of the rotator cuff muscles pass through a narrow space between the acromion process of the scapula, bursa and the head of the humerus.

Any obstruction or narrowing of this space can cause the tendons and muscles to be caught, irritating the bursa and producing pain. Similarly, if the muscles are already injured from another process, any

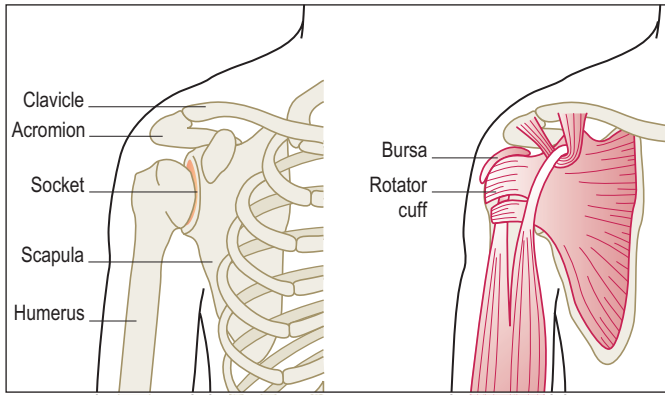

FIGURE 1.19 Hawkins' test anatomy

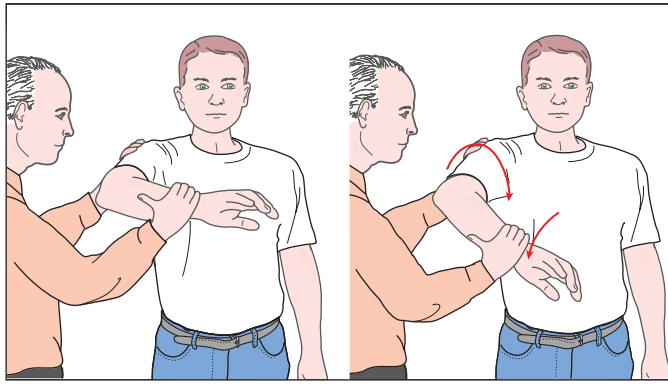

FIGURE 1.20 Hawkins' test

irritation caused by the rubbing movement in this small space will produce pain.

Like Neer's test (discussed in this chapter), Hawkins' impingement test is an attempt to 'trap' damaged or inflamed rotator cuff muscles or tendons in the subacromial space (i.e. to reproduce subacromial syndrome pain). If pain is felt during this compression, the ligament or muscle is thought to be injured.

Rotator cuff injuries/tendonitis

Positive test is caused by two mechanisms:

- If the rotator cuff muscles are weak or injured, the humerus may become displaced anteriorly (as the cuff normally holds it within the shoulder joint) and cause impingement.
- Irritation of pre-existing tendon damage (regardless of initial cause) is exacerbated by being forced through a narrow space, inducing further pain.

SIGN VALUE

Like Neer's test, Hawkins' is of limited diagnostic value. It has low specificity and only modest sensitivity and may only be valuable if the pain on testing is severe.[43] Some studies have shown:

- sensitivity of 92% and specificity 26–44% for identifying rotator cuff tendonitis, NLR of 0.3[44,45]
- sensitivity of 83% and specificity 51% for identifying rotator cuff tear, NLR of 0.3.[45]

Given these results, a positive test is of little value to the examiner; a negative test has some value although it does not completely rule out underlying pathology.

Heliotrope rash

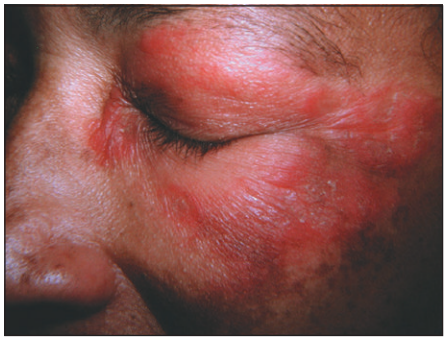

FIGURE 1.21 Heliotrope eruption seen in dermatomyositis

Reproduced, with permission, from Firestein GS, Budd RC, Harris ED et al, *Kelley's Textbook of Rheumatology*, 8th edn, Philadelphia: WB Saunders, 2008: Fig 47-10.

DESCRIPTION

Usually described as a macular, confluent, purple or purple/red rash over both eyelids and periorbital tissue. It may present with or without oedema.

CONDITION/S ASSOCIATED WITH

- Dermatomyositis

MECHANISM/S

The mechanism is undecided. There is little or no research as to why this rash occurs in dermatomyositis.

SIGN VALUE

Even though there is a paucity of research, the heliotrope (meaning purple) rash is a very valuable sign and dermatomyositis should be considered as a diagnosis.

Kyphosis

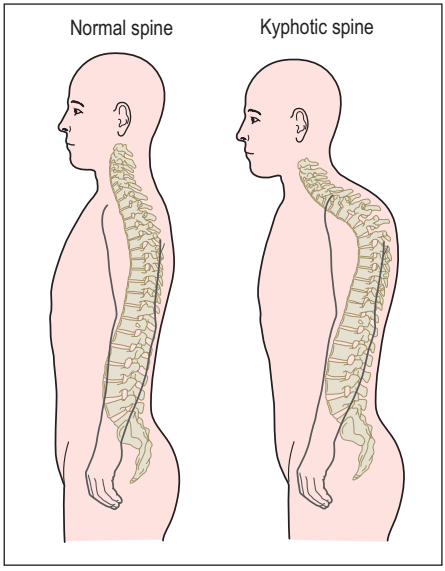

FIGURE 1.22 The normal and kyphotic spines
Note the prominent convexity of the kyphotic spine.

DESCRIPTION

Abnormally increased convexity in the curvature of the spine as seen from the side; however, kyphosis may be visible from any direction if severe enough. Often referred to in elderly females as the 'dowager's hump'.

CONDITION/S ASSOCIATED WITH

More common

- Degenerative/osteoporotic
- Traumatic

Less common

- Congenital
- Scheuermann kyphosis

MECHANISM/S

Narrowing of the anterior aspect of the vertebral body is common to most forms of kyphosis.

Degenerative/osteoporotic

In degenerative or osteoporotic kyphosis, poor posture, mechanical straining and osteoporosis may, over time, result in degeneration and/or compression fractures of the vertebrae. The anterior aspect of the vertebrae becomes narrowed relative to the posterior aspect and the kyphosis is exaggerated.

Congenital kyphosis

Congenital kyphosis results from either a *failure of formation or a failure of segmentation* of the vertebral body elements.[46]

In failure of segmentation, the anterior part of the vertebral body fails to separate from the vertebral body below, resulting in anterior fusion of the anterior aspect of the vertebrae. The posterior aspect continues to grow, causing kyphosis.[46]

Scheuerman kyphosis

The mechanism behind Scheuerman kyphosis is multifactorial.[47] Suggested influences include:

- herniation of vertebral disc material into the vertebral body, causing decreased vertebral height and increased pressure anteriorly, leading to abnormal growth and wedging of the vertebrae
- a thickened anterior ligament contributing to 'bowing' of the spine
- mechanical factors (e.g. heavy lifting over time combined with anterior ligament tightness)
- abnormal collagen matrix.

SIGN VALUE

The value in detecting kyphosis of the spine is dependent on the age of the patient and the severity of the curvature. Kyphosis in paediatric patients may be suggestive of congenital kyphosis, which can have serious complications, including damage to the spinal cord if not addressed. On the other hand, kyphosis in a very elderly patient may not warrant intervention, unless it is severe and causing complications such as neurological or respiratory problems.

Lachman's test/sign

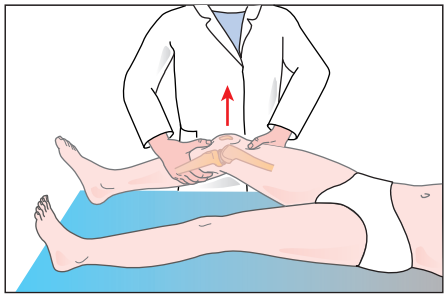

FIGURE 1.23 Lachman's test of the anterior cruciate ligament (ACL)

With a 20–30% bend at the knee, the tibia is moved forward on the femur to test the integrity of the ACL.

DESCRIPTION

With the patient lying supine with heels on the table and the knee flexed slightly (20–30°), the examiner grasps the femur just above the knee with one hand and the proximal tibia with the other. The tibia is then quickly pulled forward. If the test is negative, there will be a sudden end point to the tibia's forward movement. The test is positive if the end point is *not* quickly and abruptly reached.

CONDITION/S ASSOCIATED WITH

- Anterior cruciate ligament (ACL) injury

MECHANISM/S

The ACL arises from the lateral condyle of the femur and ends on an eminence of the tibia. It limits anterior movement of the tibia on the femur. The Lachman test is simply a matter of pulling the tibia forward against the ACL in an attempt to test its integrity. If the ACL is intact, the tibia will not be able to be jerked far forward; if it is not intact, there will be more anterior movement.

SIGN VALUE

The Lachman test is often used with the anterior drawer test to test the ACL. It is said to have higher sensitivity and is generally accepted to be a superior test of the ligament.[48]

- One summary of available studies[1] showed sensitivity of 48–96%, specificity of 90–99% and PLR of 17.0.
- Another summary of studies[49] displayed a variance in sensitivity of 60–100% with only one study within this meta-analysis testing specificity, which was found to be 100%.

Livedo reticularis

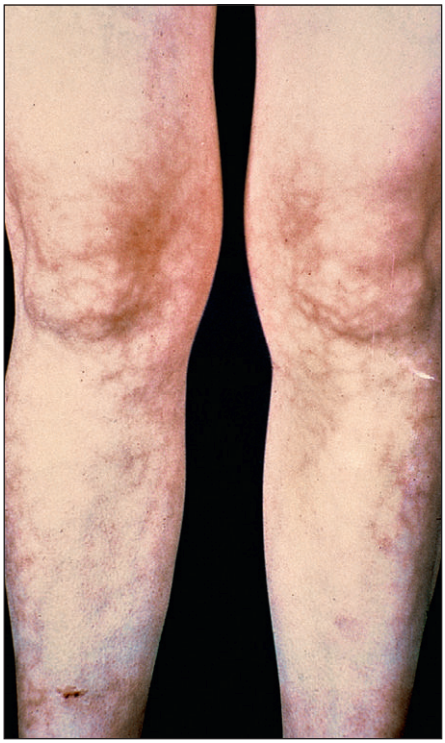

FIGURE 1.24 Livedo reticularis – a net-like pattern often erythematous or violaceous in colour

Reproduced, with permission, from Floege J et al, *Comprehensive Clinical Nephrology*, 4th edn, Philadelphia: Saunders, 2010: Fig 64-13.

DESCRIPTION

A macular, bluish/purple discolouration of the skin that has a net- or lace-like appearance.

CONDITION/S ASSOCIATED WITH

More common

- Primary or idiopathic livedo reticularis (LR)
- Elderly people

Less common

- Secondary LR

Present in numerous disorders including:

- Hypercoagulable/haematological states
  - Antiphospholipid syndrome
  - Snedden's syndrome
  - Cryoglobulinaemia
  - Multiple myeloma
  - Polycythaemia
  - DVT
  - TTP
- Vasculitis
- Connective tissue disorders (e.g. SLE, Sjögren's)
- Embolisation (e.g. cholesterol embolisation syndrome)
- Vessel wall deposition (e.g. calciphylaxis)
- Amantadine adverse effect
- Quinine adverse effect

GENERAL MECHANISM/S

LR is essentially *increased visibility of the venous plexus* of the skin. *Venodilatation of the vessels* and *deoxygenation of blood* in the plexus are the two main factors.[16]

The venous plexus of the skin is formed when arterioles arising from the dermis, perpendicular to the skin, divide to form a capillary bed. These capillaries then drain into venules and the venous plexus at the periphery of the bed.

In general, venodilatation is caused by altered autonomic nervous system function; circulating factors that cause venodilatation; or in response to local hypoxia. Venodilatation allows more venous blood to be present in engorged venules, making them larger and easier to see through the skin.

Deoxygenation is principally caused by decreased cutaneous perfusion,[50] which can be as a result of decreased arteriolar inflow or decreased venous outflow. These changes in flow are caused by:

- *decreased arteriolar inflow* – vasospasm due to cold, ANS activity, arterial thrombosis or increased blood viscosity
- *decreased venous outflow* – venous thrombosis, increased blood viscosity.

Primary or idiopathic LR

LR without the presence of underlying disease is thought to be caused by spontaneous arteriolar vasospasm, which decreases oxygenated blood inflow, causing tissue hypoxia and increased deoxygenation of venous blood.[51]

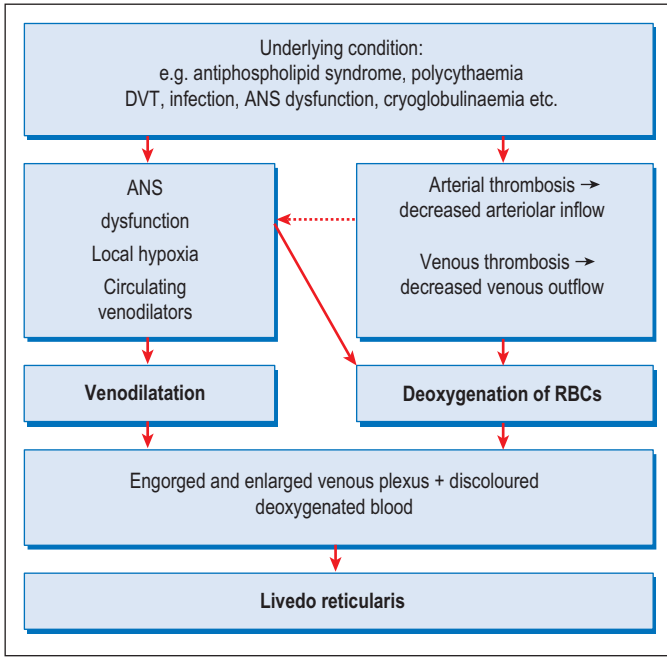

FIGURE 1.25 Mechanism of livedo reticularis

Elderly

The previous mechanisms apply to elderly patients, but with the added element of *thinning of the skin* that normally occurs with old age. This fragile skin makes it more likely that the venous plexus will be visible and, thus, that LR will be present.

Anti-phospholipid syndrome

Vascular thrombosis caused by anti-phospholipid antibodies leads to blocking of the venous or arteriolar system. This results in decreased oxygenated blood flow and increase deoxygenated blood. Vessels may also become enlarged if there is a clot stopping blood exiting the venous plexus. The vessels are more easily seen as a result.

Cryoglobulinaemia

Cryoglobulins are proteins that become insoluble and precipitate or aggregate together when the temperature drops. Because of this, the viscosity of the blood increases and there is decreased flow through vessels, as well as increased deoxygenation of the red blood cells. The combination of these elements plus thrombosis of small vessels (as a resulting of globulins aggregating together), resulting in hypoxia and dilatation of collateral vessels in the skin, is thought to result in LR.

SIGN VALUE

Despite the many potential causes, LR is still a valuable sign. Primary or idiopathic LR is a diagnosis of exclusion and other causes should be ruled out first.

- LR has been shown to have a significant relationship with anti-phospholipid syndrome in the absence of SLE, with up to 40% of patients having LR as the first sign of the underlying prothrombotic disorder.[52]
- LR in a patient with SLE has been shown to be a significant predictor of the development of neuropsychiatric symptoms of SLE.

McMurray's test

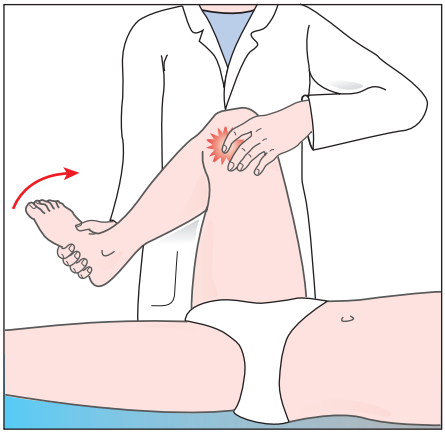

FIGURE 1.26 McMurray's test

DESCRIPTION

With the patient lying supine, the knee is acutely and forcefully flexed and rotated. The test is positive if pain or crunching or 'clunking' is felt.

Checking the medial meniscus

One hand of the examiner is placed on the posteromedial edge of the joint, while the other hand holds the foot and externally rotates it with the knee still flexed. The knee is then extended.

Checking the lateral meniscus

With one hand over the posterolateral aspect of the joint, the foot is internally rotated with the knee flexed and then extended.

CONDITION/S ASSOCIATED WITH

- Traumatic injury to meniscus
- Osteoarthritis

MECHANISM/S

The purpose of the test is to bring a torn section of either meniscus (lateral or medial) forward toward the femoral condyle and 'catch' it. By extending the knee while applying rotation, the femoral condyle is moved over the tibia and meniscus. A crunching, catching or snapping sensation will be felt by the examiner, which may or may not be painful, when the femur hits the torn meniscus.

SIGN VALUE

The evidence for McMurray's test being a useful diagnostic tool in meniscal injuries is lacking.

A meta-analysis of 11 studies[53] on its usefulness for diagnosis of meniscal injuries found McMurray's test was of little value for clinical practice. The studies analysed had significant heterogeneity in the sensitivity (10–63%) and specificity (57–98%) of the test and study design. The summarised results showed sensitivity of 48% and specificity of 86%.

Positive predictive value was positive, although again highly variable between studies (1.5–9.5).

Neer's impingement sign

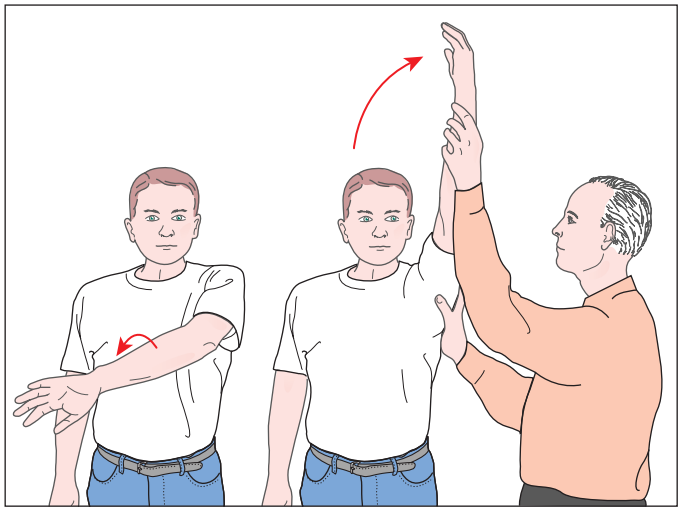

FIGURE 1.27 Neer's impingement test

DESCRIPTION

Standing next to the patient, the examiner puts one hand on the scapula of the side being tested and the arm is passively raised into full flexion with the examiner's other hand. If pain is noted, the sign is positive. Historically, the test was then supposed to be repeated after injection of local anaesthetic.

CONDITION/S ASSOCIATED WITH

- Rotator cuff tendon injury
- Subacromial bursitis

MECHANISM/S

The rotator cuff muscles (supraspinatus, infraspinatus, teres minor and subscapularis) originate from the scapula and insert onto various tuberosities of the humerus. They are designed to stabilise and hold in/depress the head of the humerus within the shoulder joint and to elevate the humerus. These muscles and tendons pass between the acromion and the humerus through a narrow space. Anything that may narrow this space (e.g. degenerative changes, spurs, anatomical changes due to overuse or abnormal muscle bulk) can cause impingement on the tendons and muscles and eventually damage and tear the tendon.

Impingement tests (of which Neer's test is one of many) depend on an attempt being made to compress the rotator cuff tendons between the head of humerus and acromion to recreate the 'impingement'.

In Neer's test, by stabilising the joint and raising the arm into full flexion, the *humerus and the rotator cuff tendons (supraspinatus tendon in particular)* and potentially some muscle are forced into contact *with the acromioclavicular ligament* and the anterior edge of the acromion, causing pain.

SIGN VALUE

A positive Neer's impingement test is of limited value in isolating the location of injury, as most types of shoulder injuries will cause pain when tested in this fashion. The test is better at ruling out possible injuries. That is, if the test is negative, it is unlikely specific injuries have occurred. Studies have shown:

- sensitivity of 75–89% and specificity 32–48% with NLR of 0.4 for identifying rotator cuff tendonitis[44,45]
- sensitivity of 88% and specificity of 43% with NLR of 0.3 for detecting rotator cuff tear.[45]

Patellar apprehension test

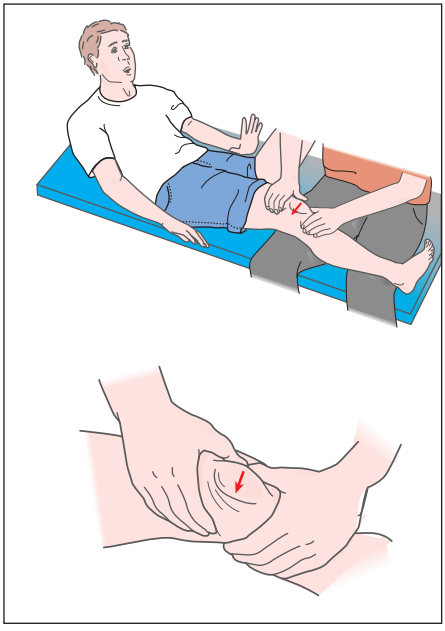

FIGURE 1.28 Patellar apprehension test

The patient experiences a sensation of the patella dislocating as a lateral force is applied to the medial edge of the patella with the knee slightly flexed.

Reprinted, with permission, from DeLee JC, Drez D, Miller MD, *DeLee and Drez's Orthopaedic Sports Medicine*, 3rd edn, Philadelphia: Saunders, 2009: Fig 22C1-5.

DESCRIPTION

The patient lies supine with the knee slightly flexed (usually to 20–30°). The examiner then applies pressure with both hands, pushing from medial to lateral on the patella, while the patient is instructed to contract the quadriceps muscle. The test is said to be positive if pain occurs or if the patient refuses to flex the quadriceps in anticipation of pain or subluxation.

CONDITION/S ASSOCIATED WITH

- Dislocated patellofemoral joint
- Patellar instability
- Patellofemoral pain syndrome

MECHANISM/S

The patella or knee cap normally rests in the patellofemoral groove, sliding up and down through this groove on flexion and extension.

It is kept in this groove by a series of tendons and ligaments, including the quadriceps tendon and patellar ligament as well as other supporting structures. If any of these structures become damaged or lax, the patella is more easily displaced out and doing so will cause pain.

By pushing laterally, the examiner is deliberately attempting to displace the patella out of the groove and, by flexing the quadriceps muscle (which moves the patella proximally), the displacement is exacerbated and more painful.

SIGN VALUE

There is a lack of evidence regarding the value of the patellofemoral test as a detector for patellar instability. One small study was completed,[54] which showed a sensitivity of only 39%. However, given that plain film and CT are static tests and are often of limited value in the acute setting and MRI is more expensive, less easily available and also questionable in the non-acute setting, physical examination is still important.

A newer test called the *moving patellar apprehension test* for lateral patellar instability has shown better sensitivity and specificity.

Patellar tap

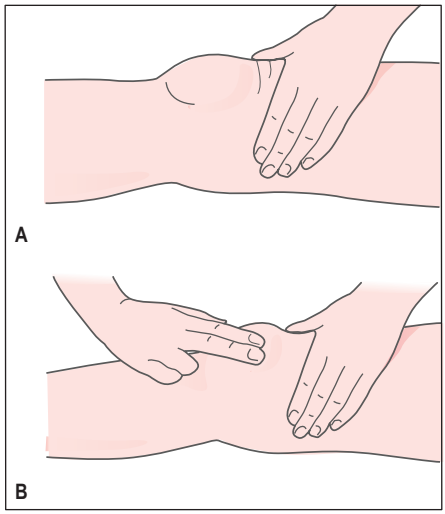

FIGURE 1.29 Patellar tap

Note that the left hand squeezes the suprapatellar pouch (**A**), while the other 'taps' the patella (**B**).

DESCRIPTION

Performed with the patient lying supine with the leg extended and flat. Pressure is placed proximal to the knee in an effort to squeeze fluid out of the suprapatellar pouch. While maintaining pressure on the pouch with one hand, with the other hand the examiner pushes down quickly on the patella to produce a palpable click as the patella hits the underlying bone. Occasionally the patella will also 'bounce' back up to the examiner's fingers.

CONDITION/S ASSOCIATED WITH

Any condition causing a knee effusion including:

More common

- Osteoarthritis
- Trauma
- Arthritic disorders
- Infection
- Gout

Less common

- Pseudogout (calcium pyrophosphate deposition disease)
- Tumour

MECHANISM/S

As with the bulge test, any condition causing inflammation in and around the knee joint can result in effusion. By pushing the fluid out of the suprapatellar pouch, the patella is lifted off the knee. When pushed or 'tapped', the patella can be felt to move down through the fluid to hit the femur. In a normal knee, the patella and femur are already in contact and therefore cannot be made to click or hit together.

SIGN VALUE

Limited studies have been completed specifically looking at the patellar tap in knee effusions. The results have shown only moderate value for this sign. One small study found the sensitivity varied from 0–55% with specificity of 46–92%, depending on the clinician completing the examination.[25] In a larger study looking at effusions in traumatic knee injury seen in general practice, the sensitivity was 83%, specificity 49%, with PLR of 1.6 and NLR of 0.3.[55] The same study indicated that, although the bulge test may be able to detect a smaller effusion, the patellar test is more likely to be associated with a clinically important effusion.

Patrick's test (FABER test)

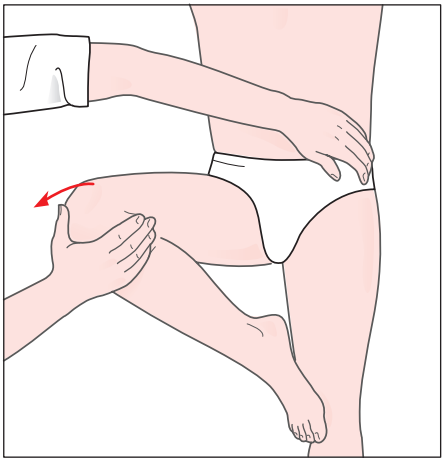

FIGURE 1.30 FABER test

DESCRIPTION

With the patient lying supine, the knee is flexed to 90° on the painful side and the foot placed on the opposite knee. The flexed knee is then pushed down by the examiner to produce external rotation of the hip. If pain is elicited in the area of the buttocks, it is considered positive for sacroiliitis, whereas pain in the groin suggests hip pathology.

FABER is a mnemonic for the movements of the hip during the test (i.e. **F**lexion, **Ab**duction, **E**xternal **R**otation).

CONDITION/S ASSOCIATED WITH

Any cause of sacroiliitis including, but not limited to:

More common

- Ankylosing spondylitis
- Psoriatic arthritis
- Reactive arthritis
- Degenerative change
- Trauma

Less common

- Arthritis associated with inflammatory bowel disease

MECHANISM/S

Inflammation of the sacroiliac joint is the main cause of this sign, whether it be from an immunological source (such as ankylosing spondylitis and other seronegative spondyloarthropathies) or simply chronic degenerative changes. This test attempts to isolate sacroiliac versus hip joint pathology by mechanically irritating an already inflamed joint.

The mechanical manipulation of the hip with flexion, abduction and external rotation is aimed at distracting the anterior part of the sacroiliac joint and compressing the posterior portion,[56] thereby eliciting pain.

SIGN VALUE

Of questionable value in isolating pain due to sacroiliitis. A review of tests of the sacroiliac joint[57] found limited sound methodological studies for the FABER test. Individual studies, however, have shown sensitivity of 69–77%[57–59] and specificity of 100%.[58]

Phalen's sign

DESCRIPTION

Paraesthesias noted in the distribution of the median nerve on maintaining flexion of both wrists to 90° that is maintained for 1 minute.

CONDITION/S ASSOCIATED WITH

- Carpal tunnel syndrome – regardless of underlying aetiology

MECHANISM/S

Exacerbation of the already increased pressure within a pathological carpal tunnel on flexion of the wrist further irritates, damages and demyelinates the median nerve.

Regardless of the underlying cause of carpal tunnel syndrome, what develops is an increased pressure within the tunnel space. When the wrist is flexed, the flexor retinaculum, which acts as a pulley on the digital flexor tendons, pulls them down onto the median nerve[60] and acutely increases pressure on the nerve.

SIGN VALUE

Phalen's test only has limited value in the diagnosis of carpal tunnel syndrome, and a negative test does not contribute to diagnostic information.[61] A review of several studies[61] has shown a wide range of sensitivities (10–91%) and specificities (33–76%), PLR of 1.1–2.1 and NLR of 0.3–1.0.

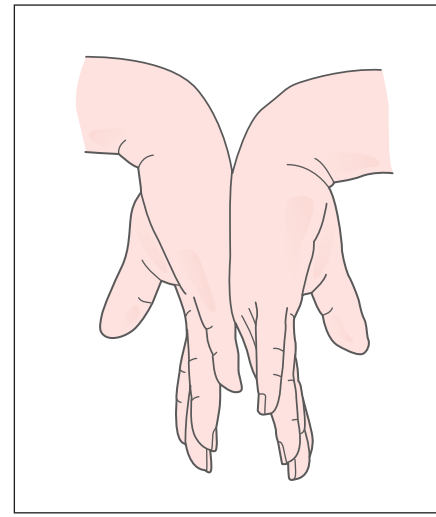

FIGURE 1.31 Hand placement in Phalen's test

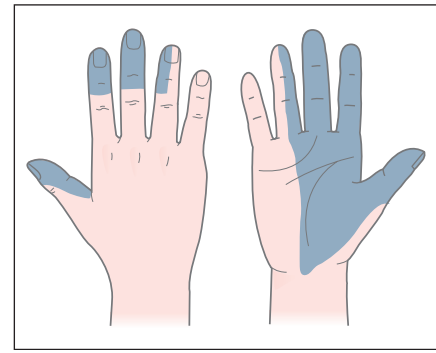

FIGURE 1.32 Median nerve distribution of paraesthesias in the hand

Proximal myopathy

DESCRIPTION

Proximal myopathy describes weakness of the proximal muscles, including the shoulder (e.g. biceps, triceps, shoulder muscles), and of the pelvic/limb girdles (e.g. the gluteus muscles, the adductors, psoas major, iliopsoas, iliacus and the lateral rotators). It can be easily demonstrated by asking the patient to rise from a seat and/or to pretend to be brushing the hair or hanging washing on the clothes line.

CONDITION/S ASSOCIATED WITH

- Non-infectious inflammatory myopathy
  - Polymyositis
  - Dermatomyositis
- Endocrine myopathy
  - Hyperthyroidism – see Chapter 7, 'Endocrinology signs'
  - Hypothyroidism – see Chapter 7, 'Endocrinology signs'
  - Cushing's syndrome – see Chapter 7, 'Endocrinology signs'
  - Hyperparathyroidism – see Chapter 7, 'Endocrinology signs'
- Systemic disorders
  - SLE
  - RA
- Genetic
  - Myotonic dystrophy
  - Spinal muscular atrophy
- Other
  - Motor neuron disease
  - Myasthenia gravis
  - Coeliac disease
  - Polymyalgia rheumatica

MECHANISM/S

Inflammatory myopathies

Inflammatory myopathies are thought to be immunologically mediated with inflammation and destruction of skeletal muscle causing weakness (Table 1.1).

Systemic disorders

Proximal myopathy may present in a number of systemic rheumatological disorders such as SLE and RA. It is thought that circulating antibody complexes, deposited in tissues and/or targeted at muscles, damage muscle fibres, resulting in weakness.

SIGN VALUE

With many different causes of proximal myopathy the sensitivity is low. There are limited studies on proximal myopathy as a sign. If true proximal myopathy is elicited, it is often pathological and should be investigated.

TABLE 1.1 Mechanisms of inflammatory myopathies

Disease	Mechanism
Polymyositis	T cell (in particular CD8) and macrophage destruction of muscle fibres
Dermatomyositis	Complement and antibody destruction of microvasculature; the deposition of complement and antibody complexes leads to inflammation and destruction of muscle fibres and hence weakness

Psoriatic nails/psoriatic nail dystrophy

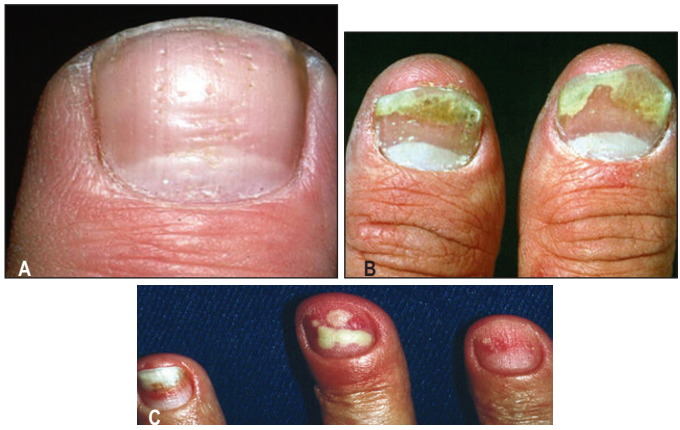

FIGURE 1.33 Nail dystrophic changes

A nail pitting; **B** onycholysis; and **C** severe destructive change with nail loss and pustule formation.

Reproduced, with permission, from Firestein GS, Budd RC, Harris ED et al, *Kelley's Textbook of Rheumatology*, 8th edn, Philadelphia: WB Saunders, 2008: Fig 72-3.

DESCRIPTION

Psoriatic nail changes refer to a number of different changes seen in nails rather than just one sign. Changes include:[62]

- Pitting of the nail plate – superficial depression in the nail surface
- Subungual hyperkeratosis under the nail plate
- Onycholysis (nail lifting) and changes in nail shape
- 'Oil drops' and 'salmon patches'
- Splinter haemorrhages

CONDITION/S ASSOCIATED WITH

- Psoriasis
- Psoriatic arthritis

MECHANISM/S

The mechanism is uncertain. It is likely a combination of genetic, environmental and immunological factors combining to develop a psoriatic lesion within the nail anatomy.

Psoriasis is thought to be a disease of abnormal immunology in which an abnormal T-cell response occurs, part of which results in an aberrant proliferation of T cells that migrate to the skin and activate and release various cytokines (e.g. IFN-γ, TNF-α and IL-2). These cytokines induce changes in keratinocytes and are also implicated in the development of the characteristic psoriatic skin lesions.[63]

Nail pitting

Nail pitting is the result of abnormal nail growth. The nail matrix is made up of, and creates, keratinocytes, which generate keratin that results in the production of the nail plate. As new cells are produced, the older cells are pushed forward and hence 'grow' the nail.

In psoriatic nails, there is a psoriatic lesion within the nail matrix that consists of parakeratotic cells that disrupt normal keratinisation and nail production. These

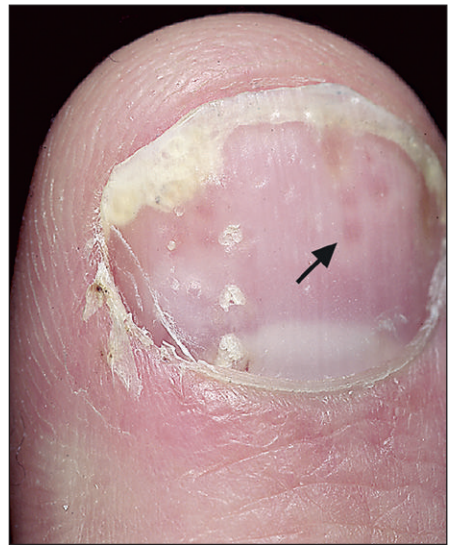

FIGURE 1.34 'Oil drops' under the nail

Reproduced, with permission, from Habif TP, *Clinical Dermatology*, 5th edn, Philadelphia: Mosby, 2009: Fig 8-23.

abnormal parakeratotic cells group together and then get sloughed off as the nail grows, leaving a depression in the nail plate.[62,64]

Subungual keratosis

Excessive proliferation of keratinocytes under the nail plate leads to accumulation of keratotic cells. This often leads to a raised and thickened nail plate.[63]

Oil drops

Thought to be caused by the accumulation of neutrophils that become visible through the nail plate.

Salmon patches

Focal hyperkeratosis of the nail bed and altered vascularisation.[62]

Splinter haemorrhages

See Chapter 3, 'Cardiovascular signs'.

SIGN VALUE

Skin and joint symptoms are the most prominent symptoms in psoriasis and psoriatic arthritis, respectively. However, older studies suggest that nail changes may be present in up to 15–50%[65] of cases of psoriasis or have a lifetime prevalence of 80–90%.[66] Interestingly, they are more commonly seen in psoriatic arthritis (75–86%[67–70]), although it is not clear whether this is a prognostic sign.

Raynaud's syndrome/phenomenon

DESCRIPTION

Most people equate Raynaud's syndrome with a blue discolouration of the fingers or toes in response to cold or stress. However, it actually has three 'colour' phases:

1. white – associated with vasoconstriction of the blood vessels
2. blue – when the distal extremities become cyanosed
3. red – after the attack passes, when blood flow is restored and hyperaemia results.

CONDITION/S ASSOCIATED WITH

Common

- Primary Raynaud's syndrome
- Secondary to other conditions
  - Scleroderma
  - SLE
  - Atherosclerosis

Less common

- Buerger's disease
- Vasculitic disorders
- Sjögren's syndrome
- Dermatomyositis

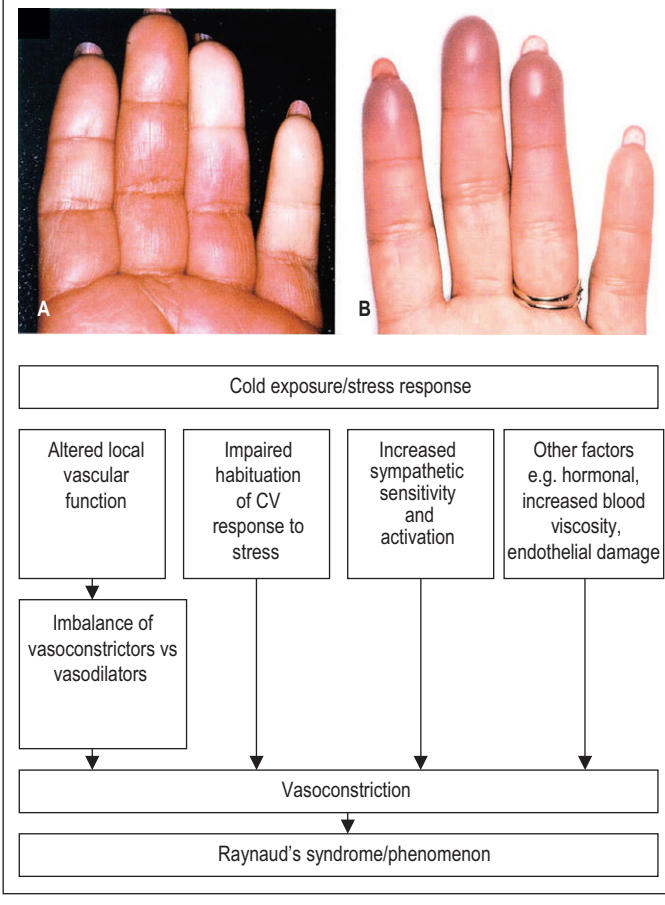

FIGURE 1.35 Raynaud's phenomenon

A Sharply demarcated pallor of the distal fingers resulting from the closure of the digital arteries. **B** Cyanosis of the fingertips.

Reproduced, with permission, from Kumar V, Abbas AK, Fausto N, Aster J, *Robbins and Cotran Pathologic Basis of Disease, Professional Edition*, 8th edn, Philadelphia: Saunders, 2009: Fig 11-28.

- Polymyositis
- Medications (e.g. beta blockers)
- Rheumatoid arthritis
- Hypothyroidism

MECHANISM/S

Raynaud's syndrome at its simplest is an exaggerated vasoconstrictive response to cold or emotion, causing transient cessation of blood flow to the toes and fingers.[71–74]

The cause of this abnormal vasoconstrictive response is multifactorial.

1. *Increased sympathetic nerve activation (centrally and peripherally mediated)* – in response to cold temperatures or stressful situations, patients with Raynaud's phenomenon will have increased sympathetic nerve activation, leading to vasoconstriction of the arteries in the toes and fingers. In contrast to normal individuals, the Raynaudian patient has an increased number of alpha-2-adrenoreceptors, which are more sensitive and more active on the smooth muscle cells of arteries, resulting in exaggerated vasoconstriction.[71–74]
2. *Impaired habituation of the cardiovascular response to stress* is also thought to contribute. Habituation is the lessening of a response to a stimulus over time. In normal individuals, ongoing exposure to a stress results in habituation, decreasing the stress response. There is evidence that this does not occur in Raynaud's, i.e. when a stress stimulus is experienced, there is a marked vasoconstrictive reaction each time.[71,72]
3. *Local vascular function fault* – an imbalance between local vasoconstrictive factors (endothelin, 5-HT, thromboxane [TXA] and other cyclo-oxygenase [COX] pathway products) and vasodilatory factors (nitric oxide [NO])[71,72] may also exist in the Raynaud's patient.
   - Local endothelin may not produce enough NO for vasodilatation.[72]
   - Repeated vasospasm causes oxidative stress and reduced NO production, thus decreasing vasodilatation.[71]
   - Inappropriately greater production of endothelin and thromboxane (TXA_2) in response to cold also occurs, leading to marked vasoconstriction.[71,72]
   - In some studies, a higher than normal endothelin-1, a potent vasoconstrictor, was seen in patients with primary Raynaud's syndrome.[72]
4. Other factors – there is evidence an array of other factors may play a role. Some of these include:
   - oestrogen – causing sensitisation of vessels to vasoconstriction[71,72]
   - increased blood viscosity[72]
   - decreased amounts of calcitonin gene-related peptide (CGRP) neurons – impairing normal nerve sensitivity, activation and vasodilatation[72]
   - endothelial damage.

Secondary Raynaud's

Structural vascular abnormalities (in addition to the factors outlined above) are thought to play a role in Raynaud's phenomenon that is secondary to an underlying disease process.

In systemic sclerosis (scleroderma), it is thought the abnormal proliferation of intimal cells (as part of the disease) causes endothelial cells to become damaged. Abnormal endothelial cells then exacerbate vasospasm by:[72,74]

- perturbing smooth muscle cells, causing them to proliferate and contract
- enhancing pro-coagulant activity and inhibitors of fibrinolysis thus promoting microthrombi
- promotion of inflammation through release of adhesion factors.

Other factors thought to contribute in systemic sclerosis include:[72]

- raised levels of angiotensin II – a vasoconstrictor
- lack of compensatory angiogenesis to meet the demands of proliferated intima – leading to ischaemia.

Saddle nose deformity

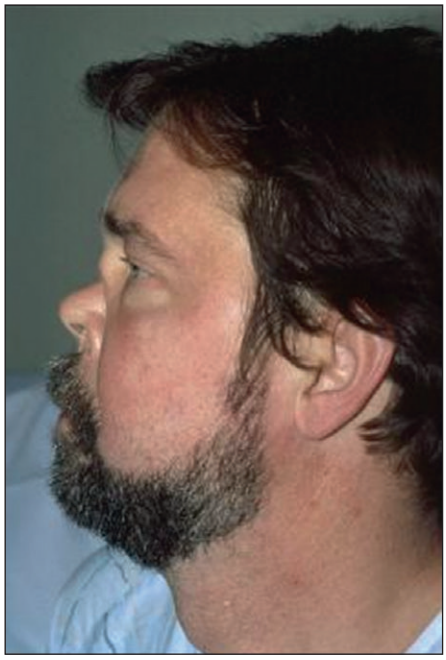

FIGURE 1.36 Saddle nose deformity

Reproduced, with permission, from Firestein GS, Budd RC, Harris ED et al, *Kelley's Textbook of Rheumatology*, 8th edn, Philadelphia: WB Saunders, 2008: Fig 82-5.

DESCRIPTION

Collapse of the middle section of the nose relative to the tip and dorsum (i.e. the nose is saddle–shaped).

CONDITION/S ASSOCIATED WITH

More common

- Trauma
- Previous nasal surgery

Less common

- Wegener's granulomatosis
- Relapsing polychondritis
- Sarcoidosis – rare
- Crohn's disease – rare
- Cocaine use – rare
- Congenital syphilis – rare

MECHANISM/S

Destruction of the septum or support cartilages is the common final pathway in the mechanism. Direct trauma or previous surgery may directly affect the integrity of the support structures, resulting in the collapse of the middle section of the nose.

Wegener's granulomatosis

Wegener's granulomatosis is an autoimmune vasculitic disorder characterised by necrotising granulomas affecting the small blood vessels of the upper and lower airways. Although the exact pathogenesis is unknown, it is thought that immune complex deposition or an autoimmune response against self antigens results in inflammation and damage/destruction of the vessels and their surrounding structures. In this sign, autoimmune destruction of the cartilage of the upper airway and nose causes the change.

Relapsing polychondritis

The aetiology of polychondritis is unknown. It is suggested that the immune system may play a role in the destruction of cartilage – in particular auricular and nasal cartilage. As for Wegener's granulomatosis, the destruction of the nasal cartilage results in the saddle nose deformity.

SIGN VALUE

This is a valuable sign. If trauma or previous surgery is absent on history, further investigation into an underlying inflammatory cause may be necessary. Nasal involvement is seen in up to 65% of relapsing polychondritis, and 9–29% patients with Wegener's granulomatosis[24] will develop a saddle nose deformity.

Sausage-shaped digits (dactylitis)

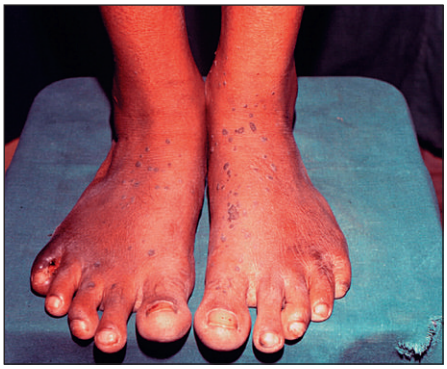

FIGURE 1.37 Sausage-shaped digits (dactylitis) in a patient with psoriatic arthritis

Reproduced, with permission, from Tyring SK, Lupi O, Hengge UR, *Tropical Dermatology*, 1st edn, London: Churchill Livingstone, 2005: Fig 11-16.

DESCRIPTION

'A uniform swelling such that soft tissues between the metacarpophalangeal and proximal interphalangeal, proximal and distal interphalangeal, and/or distal interphalangeal joint and tuft are diffusely swollen to the extent that the actual joint swelling could no longer be recognized'.[75]

Or, more simply, fingers or toes that are so swollen they look like sausages.

CONDITION/S ASSOCIATED WITH

More common

- Psoriatic arthritis
- Ankylosing spondylitis
- Reactive arthritis

Uncommon

- Tuberculosis
- Gout
- Sarcoidosis
- Sickle cell anaemia

MECHANISM/S

Spondyloarthritis

Recent studies have shown dactylitis to be caused by marked inflammation of the flexor tendons, with synovitis (tenosynovitis) and tissue swelling[76] probably resulting from the invasion of immunological factors and cytokines related to the underlying spondyloarthropathy.

An alternative hypothesis is that enthesitis (inflammation of the sites where tendons attach to the bone) is the primary lesion in the spondyloarthropathies and that synovitis of surrounding structures is a result of pro-inflammatory cytokines along the tenosynovial sheaths.[77]

Tuberculosis dactylitis

A variant of tuberculous osteomyelitis whereby TB granulomas invade the short tubular bones of the hands and feet and then the surrounding tissues, causing inflammation and swelling.[76]

Syphilitic dactylitis

A manifestation of congenital syphilis where the syphilitic spirochetes invade perichondrium, bone, periosteum and marrow and, thereby, inhibit osteogenesis. Inflammation from the invasion is another contributing factor to pain and swelling of the digits.[76]

Sarcoid dactylitis

Sarcoid non-caseating granulomas invade bone and soft tissue causing swelling and inflammation.[76]

Sickle cell dactylitis

In sickle cell anaemia, gene mutation causes a change in an amino acid so that the haemoglobin S becomes rigid and 'sickle'-shaped under hypoxic conditions. This abnormality does not permit the normal flow of red blood cells and results in obstruction in small capillaries and ischaemia in the small carpal and tarsal bones of the hands and feet.

SIGN VALUE

Sausage-shaped digits are a valuable sign. A number of studies have looked at dactylitis, and findings include:

- It is a highly specific sign for the detection of spondyloarthropathy with sensitivity and specificity, respectively, of 17.9% and 96.4%.[78]
- Clinical examination identifying dactylitis was 100% sensitive and specific for tenosynovitis when compared with MRI.[79]

- Development of dactylitis may be a marker for progression of psoriatic arthritis.[80]
- It occurs in 16–24%[81] of reported cases of psoriatic arthritis, with lifetime incidence and prevalence of 48% and 33%, respectively.[80]
- It is seen in only 4% of tuberculosis[76] cases.

Sclerodactyly

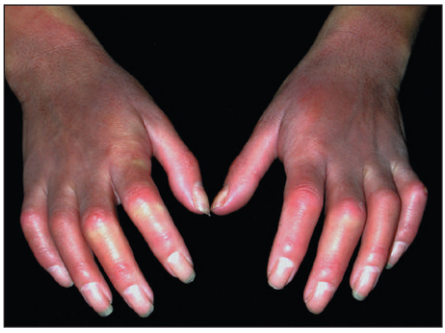

FIGURE 1.38 Sclerodactyly with flexion contractures

Reproduced, with permission, from Firestein GS, Budd RC, Harris ED et al, *Kelley's Textbook of Rheumatology*, 8th edn, Philadelphia: WB Saunders, 2008: Fig 47-12.

DESCRIPTION

Thickening and tightening of the skin of the fingers and toes.

CONDITION/S ASSOCIATED WITH

- Scleroderma (systemic sclerosis)

MECHANISM/S

The underlying aetiology and pathophysiology causing scleroderma is uncertain.

What is known is that immune cells, in particular T cells, infiltrate the skin and set in motion a cascade of events including *abnormal fibroblast and growth factor stimulation*. This in turn leads to increased production of *extracellular matrix, fibrillin and type 1 collagen* and other factors. Ultimately, these replace the normal structure of the skin, which becomes tight and fibrosed and visibly abnormal to the naked eye.

SIGN VALUE

There is limited evidence on the sensitivity and specificity of sclerodactyly as a sign. However, it may help in identifying different subsets of scleroderma. Skin thickening is seen more often in diffuse scleroderma (27%) than in limited disease (5%).[82]

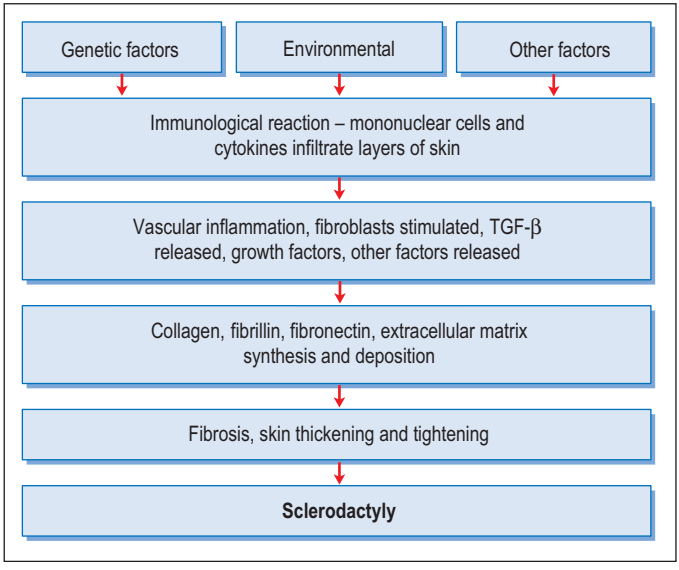

FIGURE 1.39 Proposed mechanism of sclerodactyly

Shawl sign

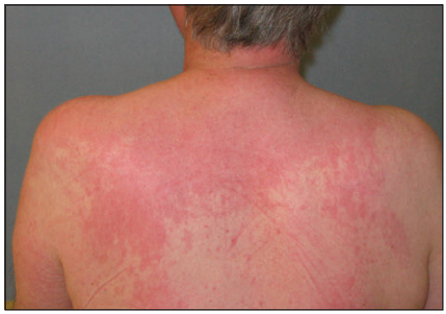

FIGURE 1.40 Shawl sign

Note discolouration over the posterior shoulder and neck.

Reproduced, with permission, from Hochberg MC et al, *Rheumatology*, 5th edn, Philadelphia: Mosby, 2010: Fig 144-7.

DESCRIPTION

Confluent, violaceous, macular (i.e. flat with violet/purple colouring) rash over the posterior shoulders and neck.

CONDITION/S ASSOCIATED WITH

- Dermatomyositis

MECHANISM/S

See 'V-sign' in this chapter.

SIGN VALUE

Although not pathognomonic, the shawl sign is highly characteristic of dermatomyositis. There is little evidence for its sensitivity and specificity in diagnosis.

Simmonds–Thompson test

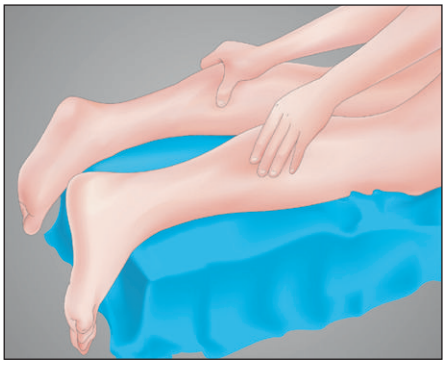

FIGURE 1.41 Simmonds–Thompson test

The calf muscles are squeezed, and the test is positive if there is no ankle plantarflexion.

DESCRIPTION

With the patient lying prone on the exam table with the ankles hanging over the end, the examiner firmly squeezes the calf muscle. The test is considered positive if no movement in the ankle (i.e. plantarflexion) can be elicited.

CONDITION/S ASSOCIATED WITH

- Rupture of the Achilles tendon

MECHANISM/S

Normally, squeezing of the calf would result in 'deformity' of the main part of the soleus muscle. This would lead to the gastrocnemius tendon moving away from the tibia, pulling the heel up and causing plantarflexion.[83]

If the Achilles tendon is not intact, this levering action cannot occur, as the Achilles is not effectively attached to the calcaneus, or heel, and so cannot lift the heel up when the soleus is compressed.

SIGN VALUE

There is little evidence available, although a positive test is generally thought to be pathognomonic for a complete rupture of the Achilles tendon.

Although this test was once thought to indicate a complete rupture of the soleus attachment to the Achilles tendon, one small recent study suggested that rupture of the gastrocnemius may also produce a positive result.

Speed's test

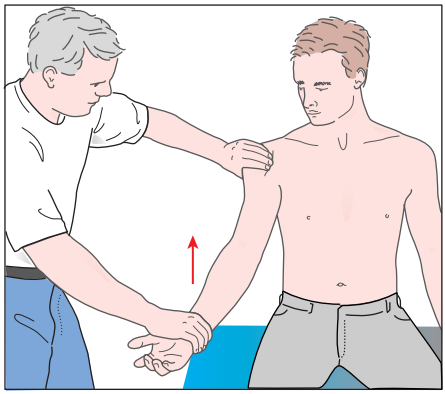

FIGURE 1.42 Speed's test

The examiner actively resists the patient lifting the extended arm.

DESCRIPTION

The patient sits or stands with his/her arm out at 60° with the elbow extended and the palm facing up (supinated). The examiner adds resistance and the patient attempts to lift the arm up against opposition. The test is positive if pain occurs on the attempt.

CONDITION/S ASSOCIATED WITH

- Biceps tendon inflammation/ subluxation
- Rotator cuff/subscapularis damage
- SLAP lesion (Superior Labral tear from Anterior to Posterior) – an injury of the glenoid labrum

MECHANISM/S

As in Yergason's test, when the biceps muscle and tendon are flexed, any pre-existing inflammation and/or damage will be exacerbated on resistance. Additionally, the subscapularis (the main supinator of the arm) is also tested with resistance. The long head of the biceps runs under fibrous tissue that is an extension of the subscapularis. This helps keep the long head of the biceps tendon within the bicipital groove. If this fibrous tissue is damaged or torn, the tendon can sublux out of the groove and further irritate the damaged fibrous tissue and the subscapularis muscle itself.

SIGN VALUE

A review of tests for biceps injury and SLAP lesions, including Speed's test, found only one study that was methodologically sound. The evidence for Speed's test, although slightly better than that for Yergason's, was still not impressive with sensitivity of 43% and specificity of 75%, with PLR of 2 and NLR 0.73.[84]

Subcutaneous nodules (rheumatoid nodules)

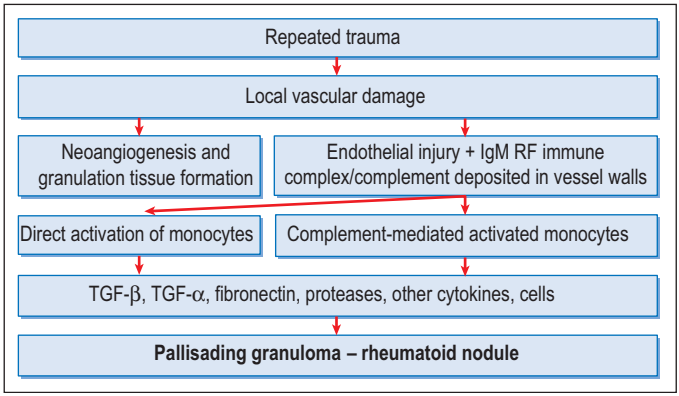

FIGURE 1.43 Mechanism of rheumatoid nodule formation

DESCRIPTION

Visible and palpable subcutaneous nodules, which are usually present over bony prominences and more evident on extensor surfaces.

CONDITION/S ASSOCIATED WITH

- Rheumatoid arthritis

MECHANISM/S

The exact mechanism is uncertain, although it is thought that a Th-1 mediated inflammatory mechanism is central to the process.[85]

The theory is that repeated trauma over the pressure points of the body, such as the elbows, stimulates local vessel damage that then leads to new blood vessel growth and granulomatous tissue formation. Endothelial injury results in accumulation of immune complexes in vessel walls, which then directly or via the complement pathway stimulates monocytes to secrete IL-1, TNF, TGF-β, prostaglandins and other factors, including proteases, collagenases and fibronectin, that ultimately lead to angiogenesis, fibrin deposition and necrosis of the connective tissue matrix, and formation of the characteristic rheumatoid nodule.[86]

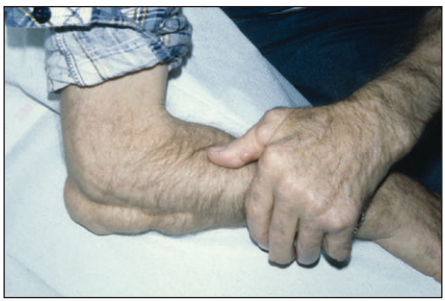

FIGURE 1.44 Large rheumatoid nodules are seen in a classic location along the extensor surface of the forearm and in the olecranon bursa

Reproduced, with permission, from Goldman L, Ausiello D, *Cecil Medicine*, 23rd edn, Philadelphia: Saunders, 2007: Fig 285-9.

SIGN VALUE

Rheumatoid nodules are an obvious and valuable clinical sign. Although only seen in 20–25% of seropositive RA, they are the most common extra-articular manifestation of the disease. Frequency of development of nodules has been shown to be correlated directly with rheumatoid factor titres and more aggressive forms of the disease.[86]

Sulcus sign

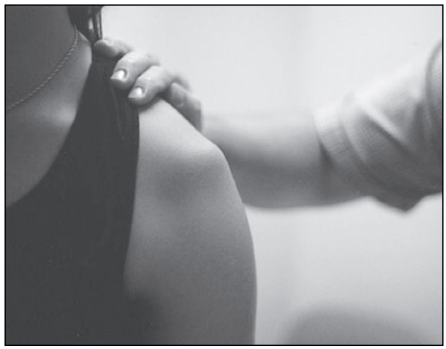

FIGURE 1.45 Sulcus sign

Note the slight dimple under the acromion.

Reproduced, with permission, from DeLee JC, Drez D, Miller MD, *DeLee and Drez's Orthopaedic Sports Medicine*, 3rd edn, Philadelphia: Saunders, 2009: Fig 17H2-16.

DESCRIPTION

With the patient's arm relaxed and hanging by the side, the examiner pulls down on the arm from the hand or elbow. Dimpling of the skin below the acromion is a positive test.

CONDITION/S ASSOCIATED WITH

- Glenohumeral joint laxity
  - Trauma
  - Muscle weakness
  - Anatomic abnormalities

MECHANISM/S

When the arm is pulled downwards in a joint with glenohumeral instability, the head of the humerus moves inferiorly relative to the glenohumeral joint. This causes pulling or 'sucking' in the skin, and a dimple over the space between the acromion and the humeral head can be seen.

SIGN VALUE

Few or no studies validating this sign have been undertaken even though it is widely used and classified.[43]

Supraspinatus test (empty can test)

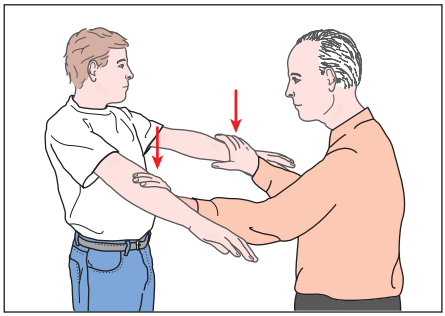

FIGURE 1.46 The supraspinatus or empty can test

DESCRIPTION

The examiner stands in front of the patient, who has the arms held up to 90° and midway between forward flexion and sideways abduction (in the plane of the scapula), as if they were about to waltz with a partner.

The patient turns the arms and hands so that the thumbs are pointing downwards – as if they were pouring a can of drink onto the ground. The examiner then tries to push the arm downwards while the patient tries to resist. The test is positive if pain occurs or if weakness is found and the patient is unable to keep the arm up against resistance.

CONDITION/S ASSOCIATED WITH

- Supraspinatus tear (rotator cuff tear)
- Supraspinatus weakness
- Rotator cuff tendonitis

MECHANISM/S

The supraspinatus muscle is responsible for abduction of the shoulder (with the deltoid). Atrophy of the muscle will cause weakness and inability to maintain the shoulder at 90°. Similarly, tears or tendonitis will produce pain on resistance and thus a positive test.

SIGN VALUE

A moderately useful test of supraspinatus function. In a summary of studies[1] the following was found:

- Pain on testing had a sensitivity of 63–85% and specificity of 52–55% for rotator cuff tear and PLR of 2.0.
- Supraspinatus testing weakness had a sensitivity of 41–84% and specificity of 58–70% for rotator cuff tear.

Swan-neck deformity

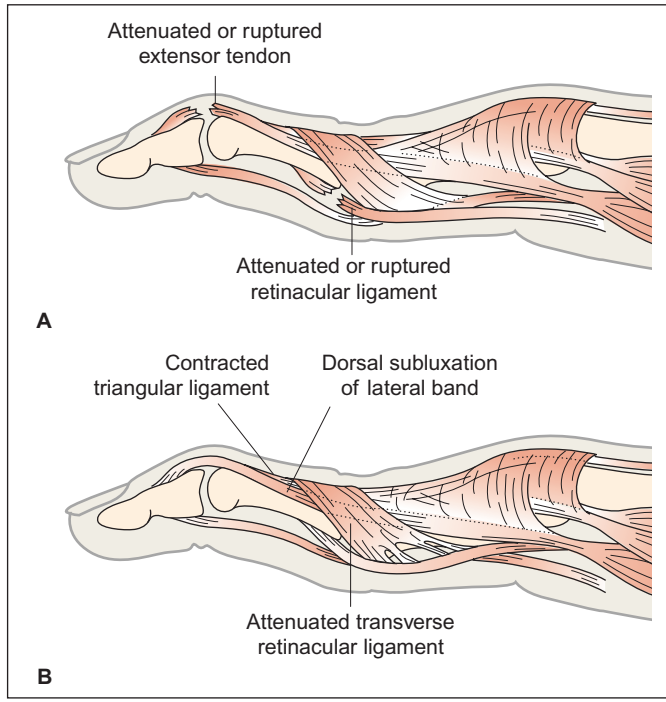

FIGURE 1.47 Swan-neck deformity pathoanatomy

A Terminal tendon rupture may be associated with synovitis of DIP joint, leading to DIP joint flexion and subsequent PIP joint hyperextension. Rupture of flexor digitorum superficialis tendon can be caused by infiltrative synovitis, which can lead to decreased volar support of PIP joint and subsequent hyperextension deformity. **B** Lateral-band subluxation dorsal to axis of rotation of PIP joint. Contraction of triangular ligament and attenuation of transverse retinacular ligament are depicted.

Based on Jupiter JB, Chapter 70: Arthritic hand. In: Canale TS, Beaty JH, *Campbell's Operative Orthopaedics*, 11th edn, Philadelphia: Elsevier, 2007: Fig 70-13.

DESCRIPTION

A deformity of the fingers in which the distal interphalangeal (DIP) joint is flexed towards the palm while the proximal interphalangeal (PIP) joint is extended away from the palm, creating a shape like a swan's neck.

CONDITION/S ASSOCIATED WITH

Common

- Rheumatoid arthritis

Uncommon

- Ehlers–Danlos syndrome
- Congenital

MECHANISM/S

A relative imbalance of intrinsic and extrinsic tendons and muscles caused primarily by the destructive effects of synovitis.[87]

A variety of changes may result in this deformity, whose basis is inflammatory disruption of the collateral ligaments, volar

plates, joint capsule or invasion of the flexor tendons.[88] The resulting pathological changes may be:

- attenuation or disruption of the extensor tendon on the distal phalanx leading to unopposed flexion – and hence the flexed DIP joint
- disruption of the retinacular ligament (which helps hold the finger in flexion), leading to unopposed extensor forces at the PIP joint and thus PIP joint hyperextension
- inflammation/synovitis causing herniation of the joint capsule, tightening of bands and tendons that limit normal movement and, in particular, PIP joint flexion.

SIGN VALUE

Physical signs of rheumatoid arthritis normally present later in the disease, and so have limited diagnostic value. If present, however, it is a useful marker of the stage of the disease – signifying that joint destruction has already taken place.

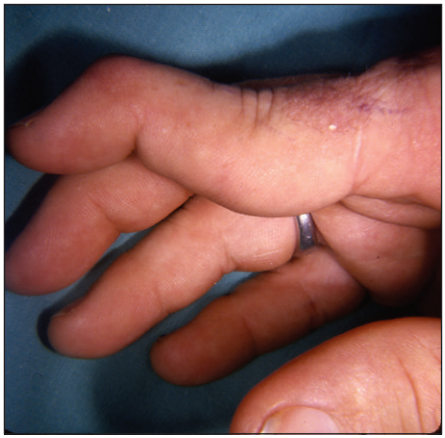

FIGURE 1.48 Swan-neck deformity

Reproduced, with permission, from Jupiter JB, Chapter 70: Arthritic hand. In: Canale TS, Beaty JH, *Campbell's Operative Orthopaedics*, 11th edn, Philadelphia: Elsevier, 2007: Fig 70-14.

Telangiectasia

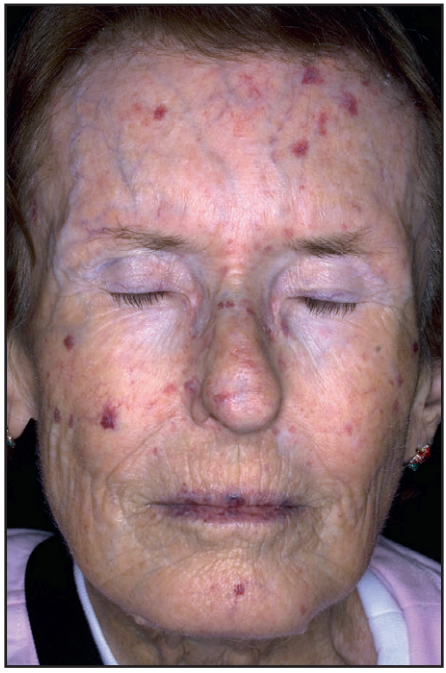

FIGURE 1.49 Telangiectasia associated with systemic sclerosis (scleroderma)

Note the skin tightening around the lips.

Reproduced, with permission, from Habif TP, *Clinical Dermatology*, 5th edn, Philadelphia: Mosby, 2009: Fig 17-30.

DESCRIPTION

Permanent dilatation of pre-existing small blood vessels, creating red lesions on the skin. Telangiectasia may present as a fine red line or a punctum (dot) with radiating lines.[40]

CONDITION/S ASSOCIATED WITH

There are numerous conditions associated with telangiectasia, including but not limited to those listed in Table 1.2.

GENERAL MECHANISM/S

It is not feasible to discuss each individual mechanism for the development of telangiectasia in this book. The key to the majority of forms is *persistent dilatation of small capillaries*. The exception to this is hereditary haemorrhagic telangiectasia, as these lesions are actually *AV malformations*.

Hereditary haemorrhagic telangiectasia (HHT)

HHT is an autosomal dominant disorder with the abnormal development of telangiectasias and AV malformations, which is thought to be mediated through a genetic abnormality in proteins of the TGF-β receptor. The TGF-β pathway is known to modulate vascular architecture, matrix formation and basement membrane development,[89] abnormalities of which may produce excess friable vessels.

TABLE 1.2 Telangiectasia-associated conditions

Skin	Systemic diseases
Acne rosacea	Carcinoid syndrome
Venous hypertension	Ataxia–telangiectasia
Essential telangiectasia	Mastocytosis
	Dermatomyositis
	Scleroderma – especially periungual telangiectasia
	Lupus erythematosus
	Hereditary haemorrhagic telangiectasia
	Liver cirrhosis

Scleroderma

The underlying mechanism for telangiectasia in scleroderma is unknown. It is presumed that there is endothelial injury leading to an angiogenic response and the development of new vessels. It has been suggested that the TGF-β pathway may be involved; however, as yet evidence for this is limited.[89]

SIGN VALUE

Given the vast number of causes of telangiectasia, the ability of the sign to identify a specific disease is limited. However, certain characteristics of the lesions can assist in diagnosis.

- Periungual telangiectasia (telangiectasia next to the nails) is said to be pathognomonic for an autoimmune connective tissue disease such as SLE, scleroderma or dermatomyositis.[90]
- Broad macules with a polygonal or oval shape, known as *mat telangiectasias*, are associated with CREST syndrome and may aid in diagnosis.[90]
- The development in adulthood of telangiectasias that are located around the mucous membranes, extremities and under the nails may help in diagnosis of hereditary haemorrhagic telangiectasia.

Thomas' test

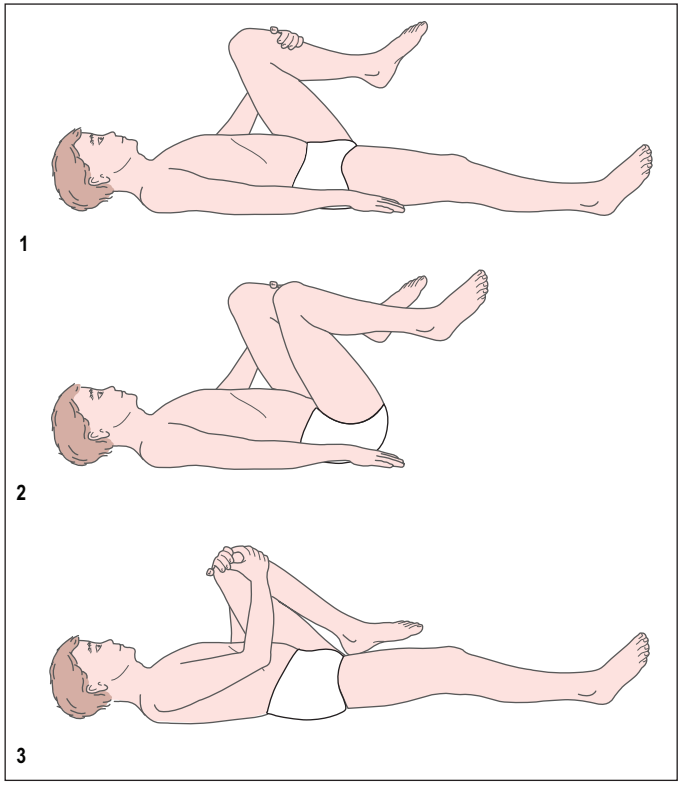

FIGURE 1.50
Performance of Thomas' test

DESCRIPTION

With the patient lying supine on the examination table, the knee and hip on the 'good' side are flexed and the knee is held against the chest. A positive test occurs if the unflexed leg rises off the table.

CONDITION/S ASSOCIATED WITH

- Hip flexion contracture/stiffness – fixed flexion deformity
- Iliotibial band syndrome

MECHANISM/S

Drawing up the knee and flexing one side of the hip rotates the pelvis upwards. In order to keep the alternate leg flat on the bed, the hip flexors and rectus femoris must be supple and stretch enough to allow the leg to lie flat. In other words, if the hip flexors are contracted, the affected leg will rise as the pelvis rotates upwards as the contracted flexors will inhibit the normal attempt at extension of the hip.

SIGN VALUE

There is limited evidence on the value of Thomas' test as a diagnostic sign.

Tinel's sign

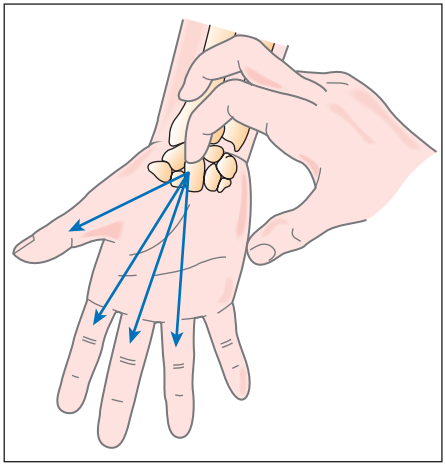

FIGURE 1.51 Completing Tinel's test

Tapping over the wrist causes pins and needles in the fingers.

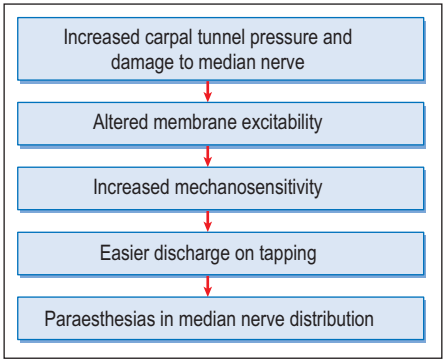

FIGURE 1.52 Mechanism of Tinel's test

DESCRIPTION

The patient will describe paraesthesias in a median nerve distribution when the examiner taps with a finger at the distal wrist crease over the median nerve. It should be noted that Tinel's original description was not specific for the median nerve but rather for the sensation of 'pins and needles' arising from any injured nerve tested in this way.

CONDITION/S ASSOCIATED WITH

- Carpal tunnel syndrome – regardless of aetiology

MECHANISM/S

Altered 'mechanosensitivity' is thought to be the underlying cause of the 'pins and needles' elicited in this test.

In carpal tunnel syndrome, there is increased pressure in the carpal tunnel and resulting damage to the median nerve. It is thought that this damage results in altered mechanosensitivity[91] of the median nerve, possibly due to an abnormally excitable membrane. So, when lightly struck through the skin, the irritated/damaged nerve discharges more readily.

SIGN VALUE

A number of studies have looked at the value of Tinel's sign. A review of studies[61] found that Tinel's sign had limited or no value in distinguishing people with carpal tunnel syndrome from those without. Studies reviewed ranged in sensitivity 25–60%, specificity 64–80%, PLR 0.7–2.7 and NLR 0.5–1.1. It is thought that Phalen's sign maybe more sensitive and specific than Tinel's.[92]

Trendelenburg's sign

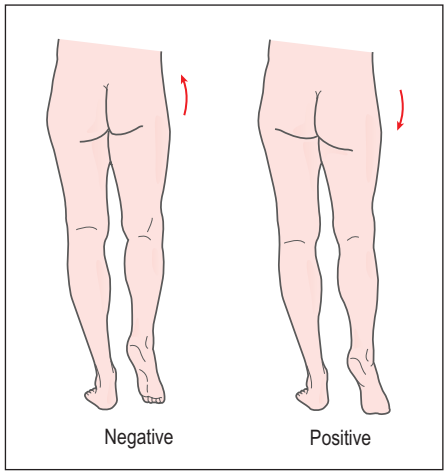

FIGURE 1.53 Trendelenburg test

Note that the positive test on the right indicates a problem with the left hip abductors – remember the sound side sags.

Based on Goldstein B, Chavez F, Phys Med Rehabil State Art Rev 1996; 10: 601–630.

DESCRIPTION

If possible, the patient is asked to stand on one leg, while the other is bent and held off the ground. For the sign to be present, the pelvis must be seen to 'drop' on the side that has the leg suspended. Confusingly, the pathology is *not* on this side (i.e. not the one with the dropped pelvis), but in the leg being stood on, hence the saying 'the sound side sags'.

CONDITION/S ASSOCIATED WITH

Any cause of hip abductor dysfunction:

- Contracted or shortened gluteus medius
- Spinal cord lesion
- Superior gluteal nerve dysfunction
- Radiculopathy
- Slipped capital femoral epiphysis

MECHANISM/S

Normally, when we stand on one leg, the abductors (in particular the gluteus medius) contract to take more weight on the standing leg side to compensate for having the opposite leg off the ground and to help maintain balance. With dysfunction of the muscle or its nerve supply (in this case the superior gluteal nerve), it is unable to contract effectively and hence does not take the additional weight, and the sound side (the side opposite to the stance leg) sags, or tilts downwards.

SIGN VALUE

There is limited evidence as to sign value and, given the number of potential causes, it is fairly non-specific. However, if identified, a positive Trendelenburg's sign should be investigated.

True leg length discrepancy (anatomic leg length discrepancy)

DESCRIPTION

The leg length is measured from the anterior iliac spine to the medial malleolus with the patient supine. There is no clear definition as to what constitutes a significant discrepancy; however, some evidence suggests that it is not clinically relevant until there is greater than 20 mm difference between legs.[93]

CONDITION/S ASSOCIATED WITH

Discrepancies in true leg length may occur in:

- Congenital disorders
- Fractures
- Post-surgical shortening
- Tumour

MECHANISM/S

True, or anatomic, leg length equality relates to the actual length of the bones and anatomical structures making up the hip and the lower limb. Therefore, any problem in the anatomy that constitutes the leg length (from the head of the femur down to the ankle mortise) may cause a discrepancy. For example, abnormalities in growth plates during development may lead to one leg being longer than the other; poorly healed fractures can also lead to a shortened leg.

SIGN VALUE

A leg length discrepancy is a non-specific sign by nature of the variety of possible causes. Furthermore, some evidence[93,94] has shown considerable inaccuracy in the clinical measurement of limbs. A number of factors, including difficulty palpating bony landmarks, iliac asymmetries masking or accentuating length discrepancies, asymmetrical position of the umbilicus (see 'Apparent leg length inequality' in this chapter), joint contractures and genu varum/valgus, are thought to make clinical measurement inaccurate.[5]

Ulnar deviation

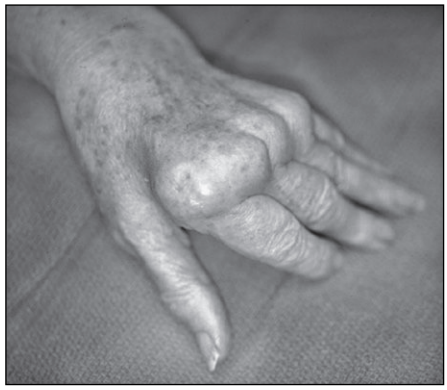

FIGURE 1.54 Ulnar deviation and subluxation

The hands show typical manifestations of end-stage erosive changes around the metacarpophalangeal joints, with volar dislocation and ulnar drift of the fingers.

Reproduced, with permission, from Firestein GS, Budd RC, Harris ED et al, *Kelley's Textbook of Rheumatology*, 8th edn, Philadelphia: WB Saunders, 2008: Fig 66-5.

DESCRIPTION

The displacement of the metacarpophalangeal and/or radiocarpal joint towards the ulnar aspect of the wrist.

CONDITION/S ASSOCIATED WITH

- Rheumatoid arthritis

MECHANISM/S

Metacarpophalangeal (MCP) joint

Destruction of the normal wrist stabilisers by synovitis and inflammation leads to an imbalance of radial and ulnar forces and ulnar deviation.

MCP joints are condylar and are able to move in two planes. They are therefore less stable than interphalangeal joints. Progressive synovitis and pannus in rheumatoid arthritis causes the initial stretching of the joint capsule and ligaments, causing instability. The actual cause or forces producing the ulnar shift are not clear but theories include:[87,88]

- normal tendency of fingers to move towards the ulnar side on flexion
- inflammation of the carpometacarpal (CMC) joints in the ring and small fingers causes further spread of metacarpals in flexion, producing an 'ulnarly' directed force on the extensor tendons
- stretching of the collateral ligaments of the MCP joints that permits volar displacement of the proximal phalanges
- stretching of the accessory collateral ligaments that permits ulnar displacement of the flexor tendons within their tunnels
- stretching of the flexor tunnels that permits even more ulnar displacement of the long flexor tendons
- ulnar displacement of the long flexor tendons caused by surgical release of their sheaths
- attenuated radial sagittal bands that allow ulnar displacement of the long extensor tendons
- rupture of long extensor tendons at the distal edge of the dorsal carpal ligament that increases the possibility of dislocation of the MCP joints
- contracture of the interosseus muscles on the ulnar side of the joint.[95]

Radiocarpal ulnar deviation

Rheumatoid-related inflammatory changes lead to progressive synovitis of the wrist joint as well as over the ulnar styloid and the scaphoid head. When the scaphoid becomes involved and unstable, there is wrist collapse, translocation of the carpus on the radius, imbalance of tendons and ulnar deviation of the MCP joints.[87]

SIGN VALUE

Ulnar deviation is a relatively specific sign of rheumatoid arthritis and useful in distinguishing it from osteoarthritis. Its diagnostic use is limited as these changes occur later in the disease so, like the swan neck deformity, its utility lies more in identifying the severity of joint changes.

V-sign

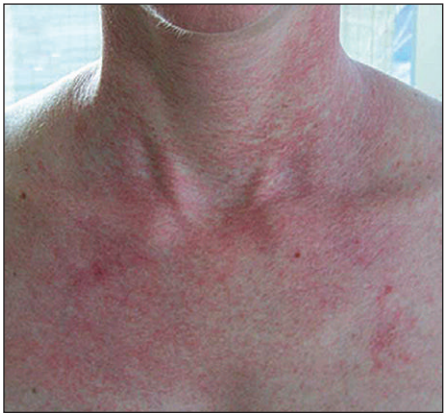

FIGURE 1.55 Irregular patchy erythema with associated prominent telangiectasias in a woman with dermatomyositis

Reproduced, with permission, from Shields HM et al, Clin Gastroenterol Hepatol 2007; 5(9): 1010–1017.

DESCRIPTION

A confluent, macular violet/red erythema seen over the anterior neck and upper chest. Often found in the V-shape of the neck of a shirt.

CONDITION/S ASSOCIATED WITH

- Dermatomyositis

MECHANISM/S

The mechanism is unclear. However, *microvascular injury* by complement deposition injury has been suggested as the pathophysiological basis.[96]

Dermatomyositis is an inflammatory myopathy characterised by microvascular damage and destruction of muscle by immunological mechanisms, principally by complement deposition but with antibody complexes also involved. Genetic predisposition, viruses and UV light are all thought to play a role in the loss of self tolerance, aberrant immunological reaction and complement and antibody deposition in muscles and micro-vessels.[97]

SIGN VALUE

Although not pathognomonic, the V-sign is highly suggestive of dermatomyositis. In up to 30% of cases, skin manifestations including the V-sign may occur before the development of the characteristic muscle weakness.

Valgus deformity

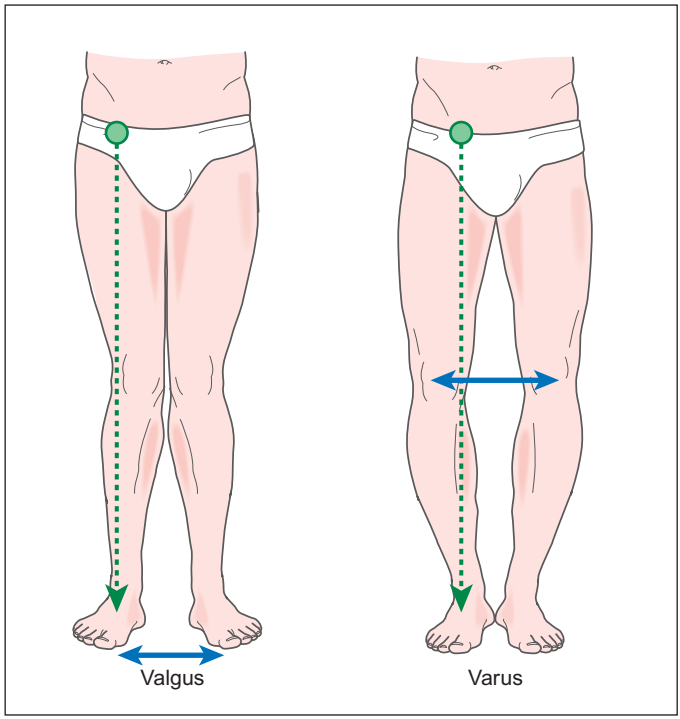

FIGURE 1.56 Examples of valgus and varus deformities of the knees

TABLE 1.3 Valgus deformity-associated conditions

Hip	Knee	Ankle	Toe
Osteochrondroses	Cerebral palsy	Paralytic	Biomechanical
	Idiopathic	Osteochrondroses	Congenital
	Blount's disease		Osteochrondroses
	Rickets		Psoriatic arthritis
	Paralytic		Multiple sclerosis
	Osteochrondrosis		Cerebral palsy
	Rheumatoid arthritis		Rheumatoid arthritis
	Osteoarthritis		Intra-articular damage
			Connective tissue disorders

DESCRIPTION

Outward displacement of the distal part of the bone or joint.

CONDITION/S ASSOCIATED WITH

Associated conditions are given in Table 1.3.

MECHANISM/S

Hallux valgus

The mechanism and factors involved in hallux valgus are complex and varied. Contrary to popular belief, it is NOT

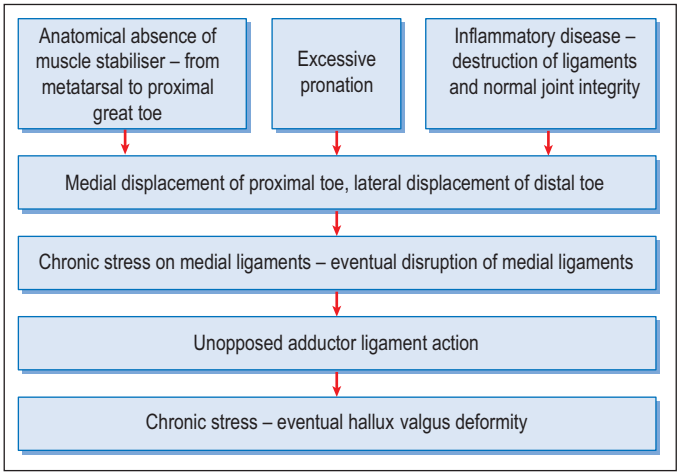

FIGURE 1.57 Factors involved in the mechanism of hallux valgus

caused by tight or ill-fitting footwear; however, different aspects of the deformity exist and footwear may exacerbate the situation.

A number of anatomical aspects of the big toe and biomechanical and pathological factors contribute to the formation of hallux valgus. Some of those identified include:[98]

- There is no muscle from the first metatarsal into the phalanx to stabilise the joint. The abductor and adductors are present but more towards the plantar surface – thus any force pushing the toe laterally is relatively unrestrained
- Owing to the anatomy of the metatarsocuneiform joint, increased pressure under the first metatarsal, for example from excessive pronation, will tend to push the first metatasal more medially relative to the proximal big toe.
- With the continued chronic stress of the metatarsal pushing medially relative to the proximal first phalanx, the medial ligament of the big toe is under pressure and may rupture – eventually allowing the adductor hallucis muscle to act unopposed on the toe, contributing to the deformity.
- Inflammatory joint disease may precipitate the formation of hallux valgus by destroying ligaments and normal joint integrity.

Knee valgus (genu valgum)

Genu valgum may be caused by a number of disorders. Basic mechanisms for a number of these conditions are shown in Table 1. 4.

SIGN VALUE

Valgus deformity has low specificity given its number of causes and is often a late manifestation of an ongoing pathological process. It is probably more valuable as an indicator of the extent of the underlying problem. For example, in vitamin D deficiency, marked valgus deformity shows a history of severe vitamin D deficiency.

TABLE 1.4 Genu valgum mechanism/s

Condition	Basic mechanism
Vitamin D deficiency	A lack of vitamin D leads to abnormal bone mineralisation, softer than normal bones, abnormal bone regrowth and bowing of the legs. Mechanical forces play a role in bone regrowth
Paget's disease	Invasion with paramyxovirus leads to abnormal activation of osteoclasts and aberrant osteoblast activity. Deformation of the bone and knee can lead to anatomical changes and valgus deformity
Cerebral palsy	Usually secondary to a hip adduction deformity caused by the cerebral palsy[47] Excessive hip internal rotation and flexed knees may exacerbate the appearance
Osteochrondrosis	Interrupted blood supply, especially to the epiphysis, leading to necrosis and then later bone regrowth – leading to abnormal formation of femur and knee joint – and eventually a valgus deformity
Paralytic disorders	Weak quadriceps, gastrocnemius and hip abductors may cause knees to enter valgus position[47]

Varus deformity

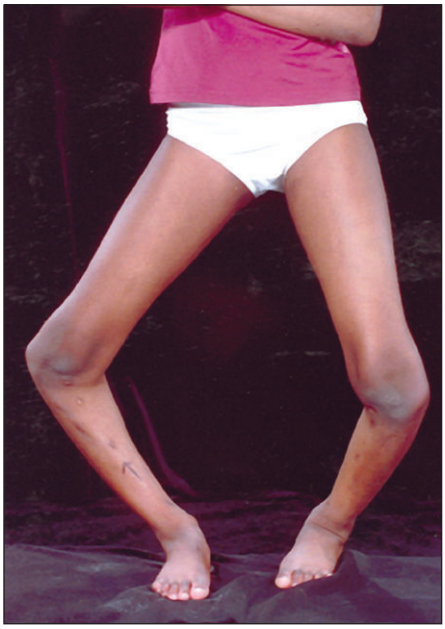

FIGURE 1.58 Bowing of both legs in infantile Blount's disease

Reproduced, with permission, from Harish HS, Purushottam GA, Wells L, Chapter 674: Torsional and angular deformities. In: Kliegman RM et al, *Nelson Textbook of Pediatrics*, 18th edn, Philadelphia: Saunders, 2007: Fig 674-8.

DESCRIPTION

Refers to the opposite of valgus deformity, i.e. the inward angulation of the distal segment of a bone or joint.

CONDITION/S ASSOCIATED WITH

Associated conditions are given in Table 1.5.

MECHANISM/S

Congenital

Congenital coxa vara may present in infancy or later in childhood. When presenting at birth, the congenital disorder is usually rare.

It is often bilateral and characterised by progressive bowing of the femur, a decreased angle between the femoral shaft and neck, and a defect in the *medial* part of the neck of the femur. This defect in cartilage and bone is exposed when the child begins to walk, with more pressure being placed on the defective femoral neck and varus deformity slowly occurring.[47]

Rickets

As for genu valgum deformity but owing to anatomical differences of the patient, the pressure on the poorly mineralised bone is placed on the femoral neck, thus causing coxa vara over time.

TABLE 1.5 Varus deformity-associated conditions

Hip	Knee	Ankle	Toe
Congenital disorders (e.g. cleidocranial dysplasia, Gaucher's disease)	Physiological – common	Trauma	Complication from bunion surgery
Perthes' disease	Blount's disease	Iatrogenic	Trauma
Development dysplasia of hip	Ricketts	Congenital	Burn injury with contracture
Slipped capital femoral epiphysis (SCFE)	Trauma		Rheumatoid arthritis
Rickets	Infection		Psoriatic arthritis
Osteomyelitis	Tumour		Charcot–Marie–Tooth (CMT) disease
Paget's disease	Skeletal dysplasia		Avascular necrosis
Trauma			

Coxa vara

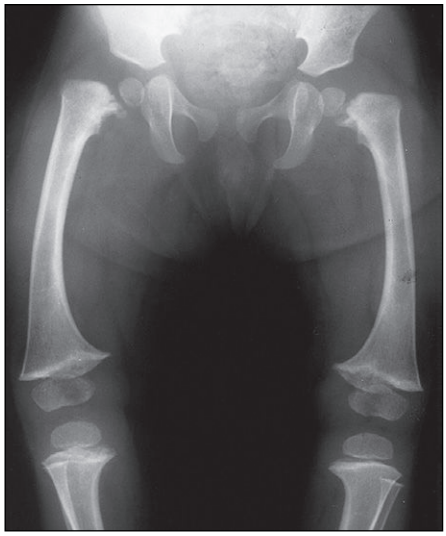

FIGURE 1.59 Metaphyseal chondrodysplasia, type Schmid

There is bilateral coxa vara, the metaphyses are splayed and irregular, and there is lateral bowing of the femora.

Reproduced, with permission, from Adam A, Dixon AK (eds), *Grainger & Allison's Diagnostic Radiology*, 5th edn, New York: Churchill Livingstone, 2008: Fig 67.13.

Perthes' disease

Although the underlying cause of Perthes' disease is unknown, there is a loss of blood supply to the femoral head. With this, the head of the femur softens and collapses. If the collapse of the femoral head occurs medially, coxa vara may result.

Genu varum

Genu varum or bow-leggedness is normal in many children up to 2 years.[99,100] It should be differentiated from Blount's disease.

Blount's disease

The underlying mechanism of genu valgum in Blount's disease is unknown. It is known that there is loss of medial tibial physeal growth that causes progressive bowing of the legs.[100] It is possible that this is secondary to compressive forces causing suppression of the medial physeal plate.[99]

Hallux varus

Hallux varus is comprised of medial deviation of the first metatarsophalangeal (MTP) joint, supination of phalanx and interphalangeal flexion or claw toe. It results from an imbalance between osseous, tendon and capsuloligamentous structures at the first MTP joint.[101]

By far the most common cause and mechanism for hallux varus is iatrogenically from surgery to correct bunions. However, most of the factors that cause hallux varus in the surgical setting are applicable to all other causes of the deformity.[101] Essentially, there is a loss of the normal balance structures of the toe precipitated by:[101]

1. loss of osseus support medially, which allows sesamoid bone and proximal phalanx to drift medially
2. overcorrection the intermetatarsal angle during surgery
3. loss or destruction of the fibular sesamoid bone, leading to instability and predisposition to clawing of the toe
4. muscle imbalance, so that the loss of support structures allows unopposed pulling of the medial muscles, particularly the abductor hallucis and part of the flexor hallucis brevis
5. aggressive bandaging that can cause the toe to become malpositioned, fibrosed and scarred.

SIGN VALUE

Like the various valgus deformities, the varus deformities are often a late sign of an underlying systemic disease and they are very specific. Further, hallux varus is rarely a sign of underlying pathology and is more likely a postsurgical issue. Having said this, varus deformities can cause significant discomfort and further medical problems for the patient if not appreciated, particularly Perthes' and other diseases that affect children.

Yergason's sign

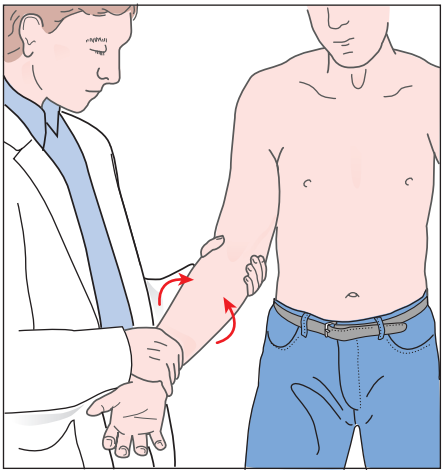

FIGURE 1.60 Yergason's sign

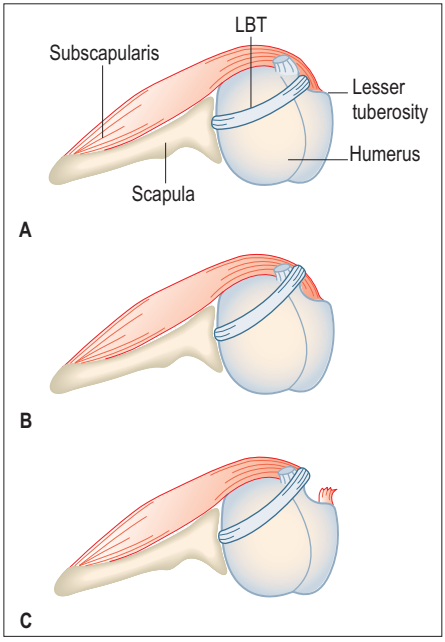

FIGURE 1.61 Yergason's sign pathoanatomy

Overhead view of the subscapularis muscle, long head of the biceps tendon (LBT) and bicipital groove. **A** Intact structure depicting normal anatomy; **B** partial tear of the subscapularis tendon from the attachment on the lesser tubercle, with the LBT subluxed over the lesser tubercle into the subscapularis muscle; **C** complete tear of the subscapularis tendon from the attachment on the lesser tubercle, with the LBT subluxed over the lesser tuberosity and the subscapularis tendon.

Based on Pettit RW et al, Athletic Training Edu J 2008; 3(4): 143–147.

DESCRIPTION

The examiner stands in front of the patient, who has the arms flexed to 90° at the elbow and the palms facing downward (pronated). The patient then tries to supinate the forearm against resistance from the examiner.

CONDITION/S ASSOCIATED WITH

- Biceps tendon damage/inflammation
- Rotator cuff tendonitis – in particular subscapularis
- Subscapularis tear

MECHANISM/S

The long head of biceps is the main supinator of the arm. Therefore, by adding resistance against supination, the muscle and tendon are stressed and any inflammation or damage is exacerbated, causing pain.

The long head of biceps travels in the bicipital groove made by the greater and lesser tuberosities of the humerus and originates on the lip of the glenoid labrum. One of the structural supports that maintains the long head of biceps in the bicipital groove is the fibrous extension of the subscapularis, which passes over the top of the long head of biceps tendon (LBT) and attaches to the two tuberosities.[102] If this fibrous extension is ruptured, the biceps tendon is able to sublux and move over the remaining extension of subscapularis, and possibly over subscapularis itself, and irritate an already inflamed area.

Rotator cuff and impingement

Subacromial impingement may produce a positive Yergason's sign by progressively wearing away at the supraspinatus tendon and exposing the underlying capsule and long head of biceps tendon, which is then subjected to the same impingement[1] and thus is damaged and inflamed.

SIGN VALUE

Yergason's sign has been evaluated for use in diagnosis of bicep tendonitis and rotator cuff and labrum injuries, and some evidence thus far has shown it to be of limited to moderate value.

- In detecting bicep tendon injuries, one study[84] of 325 patients has shown Yergason's test to be a relatively poor test with a sensitivity of 41% and only moderate specificity of 79%, NLR of 0.74 and PLR of 1.86. PPV was 0.48 and NPV was 0.74.
- A review of tests for superior labrum anterior posterior (SLAP) lesions showed Yergason's sign had a sensitivity of only 32% and specificity 75%, and the likelihood ratios could not effectively rule in or out a SLAP lesion when compared to arthroscopic results.[103]
- In detecting rotator cuff tendonitis, it has a sensitivity of only 37% and specificity of 87%, PLR of 2.8 and NLR of 0.7.

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CHAPTER 2

Respiratory Signs

RESPIRATORY SYSTEM REVISITED

Lungs aside, the respiratory system is made up of three main components: the central control centre, sensors and effectors.

The brainstem contains several centres in the pons and medulla, which (in addition to other parts of the brain) regulate inspiration and expiration. It receives information from a variety of receptors about pO_2, carbon dioxide, stretch, compliance and irritants of the lung and upper airways. The central control system sends messages via nerve fibres such as the phrenic nerve to control respiratory rate and depth, depending on the data it receives.

Damage, disruption or alterations to any of these three components (brainstem, nerves, receptors) can cause specific signs.

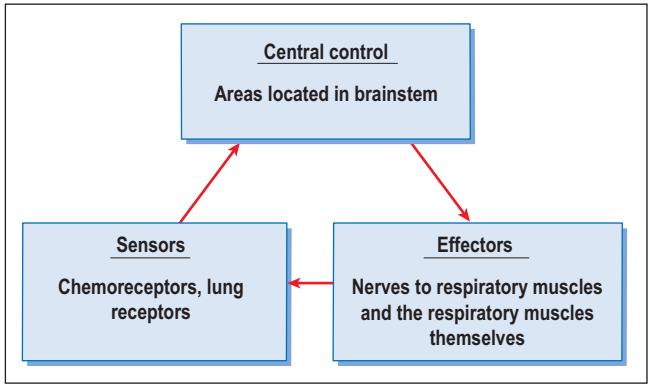

FIGURE 2.1 Simplified respiratory control

Based on West JB, *West's Respiratory Physiology*, 7th edn, Philadelphia: Lippincott Williams & Wilkins, 2005: Fig 8-1.

Accessory muscle breathing

DESCRIPTION

Normal inspiration only involves the diaphragm and expiration occurs passively due to the elastic recoil of the lungs. When inspiratory effort requires the use of the sternocleidomastoid, scalene, trapezius and internal intercostal and abdominal muscles, the 'accessory muscles' of breathing are said to be in use.

CONDITION/S ASSOCIATED WITH

Any disease resulting in an increased effort of breathing:

- Chronic obstructive pulmonary disease (COPD)
- Asthma
- Pneumonia
- Pneumothorax
- Pulmonary embolism
- Congestive heart failure (CHF)

MECHANISM/S

In times of increased respiratory effort, the accessory muscles of breathing are invoked to exaggerate the normal respiratory process. Use of the accessory muscles helps create more negative intrathoracic pressure on inspiration (pulling more air in and possibly causing *tracheal tug*) and more positive pressure on expiration (pushing air out).

On inspiration, the scalenes and sternocleidomastoid muscles help lift and expand the chest wall, allowing for a decrease in intrathoracic pressure and thus more air entering the lungs.

On expiration, the abdominal muscles help push air out of the lungs.

SIGN VALUE

The use of accessory muscles in breathing is a non-specific finding but is valuable in assessing the severity of respiratory difficulty. More than 90% of acute exacerbations of COPD present with accessory muscle use.[1] In children, accessory muscle use is a clear sign of increased respiratory effort.

Agonal respiration

DESCRIPTION

Slow inspirations with irregular pauses. Patients are often described as gasping for air. Agonal breathing is usually closely followed by death unless intervention is provided.

CONDITION/S ASSOCIATED WITH

Any aetiology leading to imminent death.

MECHANISM/S

Agonal respiration is thought to be a brainstem reflex, providing a last-ditch respiratory effort for the body to try to save itself. It is thought of as the last respiratory effort before terminal apnoea.[2]

SIGN VALUE

Without intervention, agonal respiration heralds imminent death. Studies have shown that recognition of agonal breathing may improve recognition of cardiac arrest,[3] and implementation of protocols designed to identify agonal breathing over the phone can significantly increase the diagnosis of cardiac arrest by emergency dispatchers.[4] It is absolutely a sign that, if noted, must be managed without delay.

Apneustic breathing (also apneusis)

DESCRIPTION

Apneusis (Greek *a pneusis,* 'not breathing') is characterised by prolonged periods of deep, gasping inspirations interrupted by occasional and insufficient expiration brought on by elastic recoil of the lung.

CONDITION/S ASSOCIATED WITH

- Brainstem injury

MECHANISM/S

The mechanism of apneusis is unclear but is most likely related to brainstem and, in particular, pontine dysfunction.

Apneustic breathing was thought to be caused by unopposed activity of the neurons in the lower pons, which facilitate inspiration. It is seen in patients with upper pontine lesions with bilateral vagotomy. However, more recent reports have shown that apneusis can be reproduced with midpontine lesions, ablation of the dorsal group of respiratory neurons and achondroplasia affecting the distal medulla and upper cervical spinal cord,[5] as well as in patients with normal vagal efferents.

SIGN VALUE

Given the variety of situations in which apneustic breathing may occur and its unclear mechanism, it cannot reliably be used to localise a lesion, apart from suggesting possible brainstem dysfunction. Given that it is a rare sign, there is little evidence to support its value.

Apnoea

DESCRIPTION

A cessation of breathing.

CONDITION/S ASSOCIATED WITH

Central sleep apnoea (CSA)

- Brainstem injuries – stroke, encephalitis, cervical trauma
- Congestive heart failure (CHF)
- Opiates
- Obesity-related hypoventilation syndrome (also known as Pickwickian syndrome)

Obstructive sleep apnoea (OSA)

- Obesity
- Micrognathia
- Alcohol
- Adenotonsillar hypertrophy

MECHANISM/S

Apnoeas can be classified into central or obstructive, depending on the location of the causal pathology.

Central sleep apnoea

In central apnoeas, a lack of *respiratory drive* from the respiratory centre causes a pause in breathing. There is a complex array of factors contributing to this form of apnoea.

- If injury to the brainstem ventilatory/respiratory centres (see Figure 2.1) that normally regulate breathing occurs, this can cause diminished, inconsistent or absent respiratory drive.
- Opiate medications, working via the *mu* receptors in the brainstem, decrease the central drive to breathe, even though the required networks remain intact.
- In obesity hypoventilation syndrome, it is thought that the body cannot compensate for the obstructed respiratory mechanics. This, combined with blunted chemoreceptor sensitivity, causes apnoea – although the mechanism is not clear.[6]
- Patients with motor neuron disease, myasthenia gravis, polio and other neurodegenerative diseases have a central respiratory drive but this drive does *not get transmitted* to the respiratory muscles to enable effective ventilation.
- *Cheyne–Stokes breathing* is a form of CSA and is discussed in Chapter 3, 'Cardiovascular signs'.

Obstructive sleep apnoea

The negative pressure of inspiration leads to collapse of the airway, causing a temporary obstruction or occlusion of the nasopharynx and oropharynx. Most commonly, the tongue and palate move into opposition with the posterior pharyngeal wall, causing obstruction of the airway.[7]

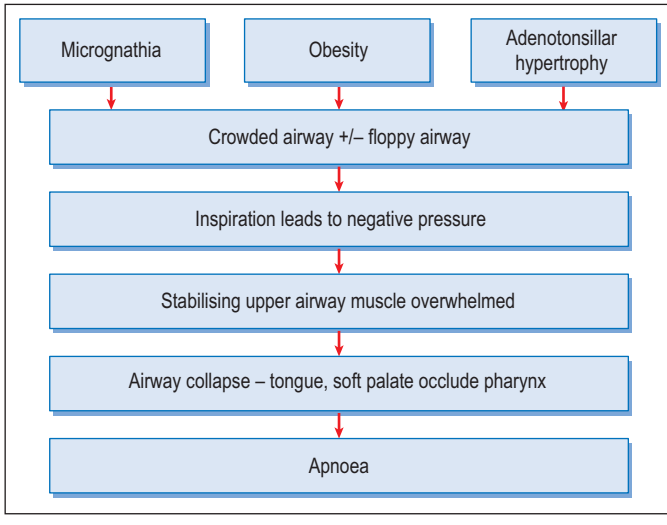

FIGURE 2.2 OSA mechanism

Anything that crowds or destabilises the airway (e.g. micrognathia, adenotonsillar hypertrophy, obesity or acromegaly) may contribute to collapse and occlusion.

Alcohol may contribute by relaxing the normal stabilising muscles of the pharynx.

SIGN VALUE

There is substantial evidence that persistent obstructive apnoeas during sleep adversely affect glucose control and blood pressure management as well as increasing the risk of stroke, coronary artery disease and heart failure, amongst numerous other complications. Apnoeas also decrease quality of sleep and increase daytime somnolence and irritability and should be suspected if these symptoms are described in context.

Asterixis

DESCRIPTION

When the patient is asked to hold the arms extended with the hands dorsiflexed, a 'flap' that is brief, rhythmless and of low frequency (3–5 Hz) becomes apparent. Asterixis may be bilateral or unilateral.

CONDITION/S ASSOCIATED WITH

More common

- Hypercapnia (e.g. CO_2 retention in COPD)
- Liver disease – see also Chapter 6, 'Gastroenterological signs'
- Renal failure

Less common

- Central nervous system (CNS) ischaemia or haemorrhage
- Drug-induced

MECHANISM/S

The mechanism for asterixis in any of the above situations is unclear. The final common pathway is equally nebulous; however, several pathological mechanism/s have been postulated:

- diffuse, widespread dysfunction of CNS function
- dysfunction of sensorimotor integration between the parietal lobe and midbrain
- episodic dysfunction of neuronal circuits involved in sustained muscle contraction due to focal or generalised neurochemical imbalance
- abnormality of the motor field in the cerebral cortex
- motor cortex pathologically slowed.

SIGN VALUE

Although not specific for a disorder, asterixis in a patient warrants investigation and correlation with other clinical signs and history.

Asymmetrical chest expansion

DESCRIPTION

When observing the patient's breathing from behind – usually by looking down at the clavicles (upper lobe movement) or by palpating with the hands wrapped around the chest wall (lower lobes) – the examiner notes uneven extension of the chest wall in inspiration or retraction on expiration. It may manifest itself as an absolute difference or a slight lag in expansion.

CONDITION/S ASSOCIATED WITH

More common

- Pneumonia
- Pleural effusion
- Flail chest
- Foreign body
- Pneumothorax

Less common

- Unilateral diaphragm paralysis
- Haemothorax
- Musculoskeletal abnormality (e.g. kyphoscoliosis)
- Neuropathy
- Pulmonary fibrosis – localised

MECHANISM/S

Symmetrical bilateral expansion of the chest wall is reliant on normal musculature, nerve function and lung compliance. Therefore, any abnormality affecting a nerve, muscle or the compliance of the lungs on a specific side of the body may produce an asymmetrical expansion.

Pneumonia, pleural effusions

In pneumonia (consolidation of the airways) and pleural effusions (fluid in the pleural space), the normal compliance of the lung is reduced. Therefore, when inspiration occurs, the affected lung will expand less than normal for any given inspiratory effort.

Foreign body

On inspiration, normal expansion of the unblocked lung occurs. However, in the blocked lung, air cannot get past the larger airways to the small airways to allow normal expansion. Hence there is a decreased opening out of the affected lung.

Flail segment

A flail chest or flail segment refers to a situation usually caused by trauma where sections of ribs become detached from the chest wall. As the segment is no longer attached to the expanding chest on inspiration, it is susceptible to negative intrathoracic pressure, which sucks the flail segment inwards on inspiration and pushes it out on expiration (opposite to the intact remaining chest wall).

Kyphoscoliosis

Progressive forward and/or lateral curvature of the spine (kyphoscoliosis) may become so severe that it mechanically depresses one lung over the other and causes decreased chest expansion on one side.

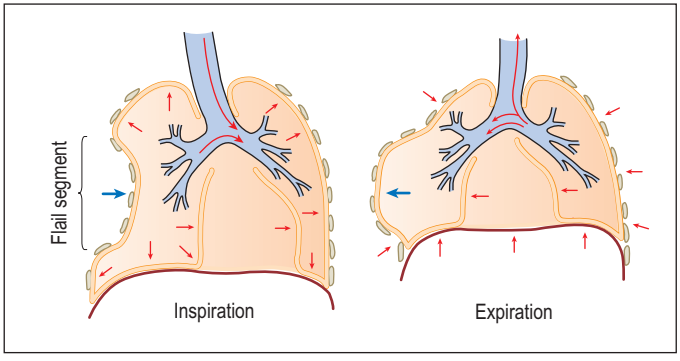

FIGURE 2.3 Flail segment mechanism

Based on Aggarwal R, Hunter A, BMJ. Available: http://archive.student.bmj.com/issues/07/02/education/52.php [28 Feb 2011].

Unilateral diaphragm paralysis

If unilateral diaphragmatic paralysis occurs for any reason, the side of the affected diaphragm will not contract, thus affecting lung expansion.

SIGN VALUE

Asymmetrical chest expansion is always pathological. While there have been very few studies, asymmetrical chest expansion was shown to be one of the most effective signs in predicting the presence of a pleural effusion, ahead of vocal resonance and vocal fremitus. It was an independent predictor of pleural effusion[8] with an odds ratio of 5.22, sensitivity of 74% and specificity of 91%.

Asynchronous respiration

DESCRIPTION

Abnormal breathing consisting of an abrupt inward motion near or at the end of inspiration quickly followed by an outward movement continuing for a variable period of time while the chest is still moving inward. The double movement is visibly irregular, but it is very difficult to identify the different elements with the naked eye.

CONDITION/S ASSOCIATED WITH

- COPD
- Respiratory distress

MECHANISM/S

Asynchronous breathing is thought to be related to the strong forced movements of the chest wall accessory muscles during forced expiration, which push the diaphragm down and the abdomen out.[9,10]

SIGN VALUE

Associated with poorer prognosis in patients with COPD[11] and increased need for mechanical ventilation.

Ataxic (Biot's) breathing

DESCRIPTION

A breathing pattern characterised by erratic rate and depth of breathing, alternating with interspersed episodes of apnoea.[12]

CONDITION/S ASSOCIATED WITH

More common

- Stroke

Less common

- Some neurodegenerative disorders (e.g. Shy–Drager syndrome)
- Meningitis
- Chronic opioid abuse

MECHANISM/S

The specific mechanism is not clear.

As in many breathing abnormalities, it is thought to be caused by disruption of the normal respiratory systems of the brainstem, in particular medullary impairment.[13]

SIGN VALUE

There is some evidence to support this breathing pattern localising pathology to the medulla. In a case series of 227 patients with medullary strokes, all but 12 experienced ataxic breathing.[14]

Barrel chest

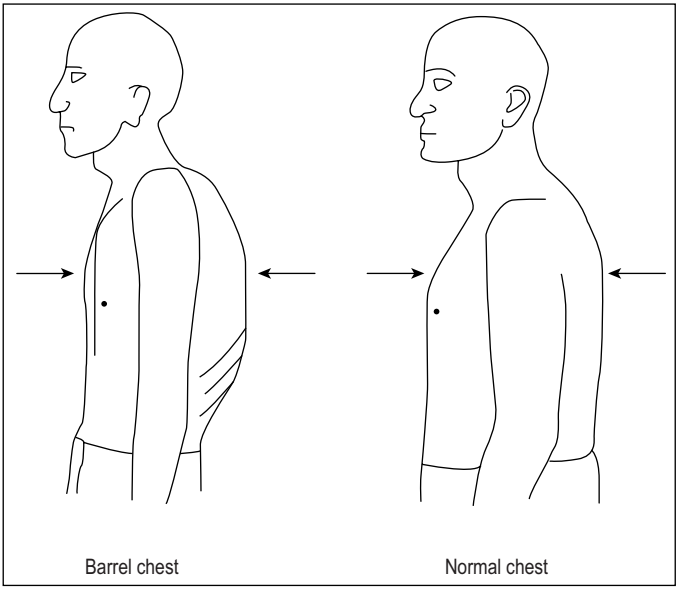

FIGURE 2.4 Barrel chest

Based on McGee S, *Evidence-Based Physical Diagnosis*, 2nd edn, Philadelphia: Saunders, 2007: Fig 25-2.

DESCRIPTION

A ratio of anterioposterior (AP) to lateral chest diameter of greater than 0.9. The normal AP diameter should be less than the lateral diameter and the ratio of AP to lateral should lie between 0.70 and 0.75.

CONDITION/S ASSOCIATED WITH

- Chronic bronchitis
- Emphysema

Also occurs in elderly people without disease.

MECHANISM/S

Considered to be due to over-activity of the scalene and sternocleidomastoid muscles, which lift the upper ribs and sternum.[9] With time, this overuse causes remodelling of the chest.

Bradypnoea

DESCRIPTION

An unusually slow rate of breathing, usually defined in an adult as less than 8–12 breaths per minute.

CONDITION/S ASSOCIATED WITH

Bradypnoea may occur in any condition or state that affects the respiratory/ventilatory centres of the brain or brainstem.

More common

- Drugs – opiates, benzodiazepines, barbiturates, anaesthetic agents
- Respiratory failure
- Brain injury and raised intracranial pressure
- Hypothyroidism
- Excess alcohol consumption

Less common

- Hypothermia
- Uraemia
- Metabolic alkalosis

MECHANISM/S

Bradypnoea can be caused by:

- decreased central nervous system output, i.e. a defect or reduction in central respiratory drive that diminishes messages 'telling' the body to breathe (e.g. brain injury, raised ICP, opiate overdose)
- disorders in the nerves connecting to the respiratory muscles (e.g. motor neuron disease)
- disorders of the muscles associated with breathing (e.g. muscle tiredness in respiratory failure)
- respiratory compensation in response to a metabolic process (e.g. in response to metabolic alkalosis, the body will reduce respiration in an attempt to retain carbon dioxide and acids).

SIGN VALUE

Although not specific, bradypnoea in an unwell patient is often a sign of serious dysfunction and requires immediate investigation. In asthma and respiratory failure, bradypnoea often precedes respiratory arrest.

Bronchial breath sounds

DESCRIPTION

Loud, harsh, high-pitched breath sounds that are normal when heard over the tracheobronchial tree but abnormal if heard over lung tissue on auscultation.

CONDITION/S ASSOCIATED WITH

- Normal over trachea
- Pneumonia – heard above area of consolidation
- Pleural effusion – heard above the actual effusion
- Adjacent to large pericardial effusion
- Atelectasis
- Tension pneumothorax

MECHANISM/S

Normally, bronchial breath sounds are not heard over the lung fields, as the chest wall attenuates higher frequencies. In the presence of consolidation, these higher frequencies are able to be audibly transmitted.[15]

SIGN VALUE

In patients with cough and fever, bronchial breath sounds suggest pneumonia (LR 3.3)[9] and are a valuable sign.

Cough reflex

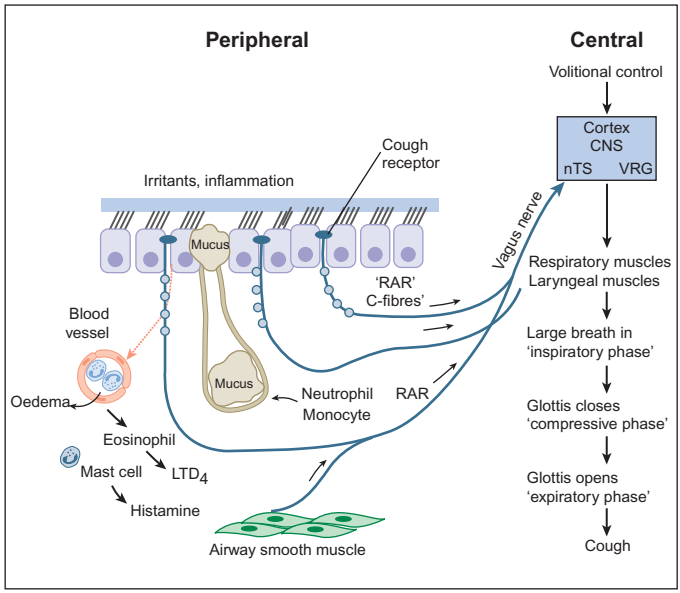

FIGURE 2.5 Cough reflex

LTD_4 = anti-leucotriene D_4

Based on Chung KF, Management of cough. In: Chung KF, Widdicombe JG, Boushey HA (eds), *Cough: Causes, Mechanisms and Therapy*. Oxford: Blackwell, 2003: pp 283–297.

DESCRIPTION

A short explosive expulsion of air.

CONDITION/S ASSOCIATED WITH

- Acute (<3–4 weeks duration)

More common

- Upper respiratory tract infection
- Common cold
- Asthma
- Inhaled particles
- Inhaled foreign body
- Bronchitis
- Aspiration
- Pneumonia
- Exacerbation of congestive heart failure
- Exacerbation of COPD
- Bronchiolitis – in children
- Croup – in children
- Pulmonary embolism

Less common

- Pertussis
- Tracheomalacia
- Vasculitis
- Chronic (>8 weeks duration)
  - Postnasal drip
  - Bronchiectasis
  - Bronchitis
  - COPD
  - Asthma
  - Gastro-oesophageal reflux disease (GORD)
  - Angiotensin-converting enzyme (ACE) inhibitor side effect
  - Interstitial lung disease

MECHANISM/S

The cough reflex may be broken down into the sensory, inspiratory, compressive and expiratory phases.

To initiate cough, vagal pulmonary receptors (made up of rapidly adapting receptors, slowly adapting receptors, C-fibres and other receptors[16]) sense mechanical and/or chemical stimulus in the airways and transmit signals back to the brainstem and cortex, initiating the cough reflex – this is the *sensory phase*. Any irritation, from inflammation of infection or chronic inflammation in COPD to direct stimulation from a foreign body or particles, is sensed and initiates the cough sequence.

During the *inspiratory phase*, a large breath in is stimulated to 'stretch' the expiratory muscles and allow them to produce greater positive intrathoracic

pressure on expiration. This allows the body to push out more air, harder and faster.[17]

In the *compressive phase*, the glottis is closed after inspiration to maintain lung volume, while intrathoracic pressure is building.

Finally, during the *expiratory phase*, the glottis opens and air is pushed out because of the high positive intrathoracic pressure.

SIGN VALUE

As cough is such a common presentation or associated sign, it is essential that it be put into clinical context in order to be valuable. If this is done, it can be of assistance in diagnosis of a condition.

- A productive cough with coloured sputum (see 'Sputum' in this chapter) is much more likely to be from an infective cause with/without underlying lung disease.
- A dry or minimally productive cough developing and lingering over months, on a background history of extensive cigarette smoking, may lead a clinician to consider lung cancer or COPD as a potential cause.
- Cough in the setting of exercise or night-induced wheeze may suggest underlying airway hyperresponsiveness and asthma.

In the setting of specific diseases, the development of cough may also suggest disease type:

- Cough as a presenting symptom in lung cancer is more often associated with central lesions within the airways where the cough receptors are located (e.g. squamous cell and small cell lung cancers).[18] It should be noted that, although cough is present in more than 65% of patients with lung cancer at diagnosis, cancer represents less than 2% of causes of chronic cough.[18]
- In an immunocompromised patient, the development of cough should raise the suspicion that opportunistic or atypical infections are present.

CHARACTER OF COUGH

Classic characteristics of cough, particularly in children, have long been described by clinicians and caregivers (as seen in Table 2.1) in order to assist diagnosis.[19]

While these descriptions may help narrow the diagnosis, data on the sensitivity and specificity of these characteristics are limited.[19]

TABLE 2.1 Classically recognised cough

Cough type	Suggested underlying process
Barking or brassy cough	Croup, tracheomalacia, habit cough
Honking	Psychogenic
Paroxysmal (with or without inspiratory 'whoop')	Pertussis and parapertussis
Staccato	Chlamydia in infants
Cough productive of casts	Plastic bronchitis/asthma
Chronic wet cough in mornings only	Suppurative lung disease

Based on Chang AB, Landau LI, Van Asperen PP et al, Med J Aust 2006; 184(8): 398–403; with permission.

Crackles (rales)

DESCRIPTION

Non-continuous, popping sounds heard more often on inspiration but which may also be heard on expiration. Coarse crackles are associated with the larger airways and finer crackles with smaller branches.

CONDITION/S ASSOCIATED WITH

There are many causes of crackles; the common ones include:

- asthma
- COPD
- bronchiectasis
- pulmonary oedema/congestive heart failure
- pneumonia
- lung cancer
- interstitial lung disease (pulmonary fibrosis).

MECHANISM/S

In all forms of crackles the accumulation of secretions with accompanying inflammation or oedema causes the airways to narrow, obstruct or even collapse.

Inspiratory crackles (which are more common) occur when the negative pressure of inspiration causes airways that have previously collapsed to 'pop' open.[20] Once open, there is a sudden equalisation of pressures on either side of the obstruction, resulting in vibrations of the airway wall, giving the characteristic sound.

Expiratory crackles are more controversial in terms of their mechanism. Two theories have been considered:

1. The 'trapped gas hypothesis' suggests that there are areas of airway collapse and that the positive pressure of expiration forces open the airways, causing crackles as they burst apart.
2. Recent studies have shown that expiratory crackles are more likely to be from sudden collapse or closure of some areas on expiration[20] (i.e. the pressures needed to keep small airways open are not maintained on breathing out and so these smaller areas collapse).

SIGN VALUE

If heard with normal breathing, crackles are most likely pathological. Various characteristics of crackles have been shown to be associated with different pathologies.

- Fine, late inspiratory crackles and pulmonary fibrosis: sensitivity 81%, specificity 86%, positive likelihood ratio (PLR) 5.9[21]
- Coarse or fine, late or pan-inspiratory crackles and congestive heart failure: PLR 3.4[22]
- Early inspiratory crackles and chronic airflow obstruction: specificity 97–98%, PLR 14.6[22]

Expiratory crackles are a lot less common, especially in COPD, but are not specific and are seen in many other lung complaints.

Dyspnoea

DESCRIPTION

Strictly a symptom and not a sign, dyspnoea is a subjective awareness that an increased amount of effort is required for breathing.

CONDITION/S ASSOCIATED WITH

- Respiratory disorders – COPD, pulmonary fibrosis, pneumonia
- Cardiac disorders – heart failure
- Anaemia
- Bronchoconstriction
- Deconditioning

GENERAL MECHANISM/S

The mechanism of dyspnoea is complex and can involve many parts of the respiratory control system. It is summarised in Figure 2.6. It can be divided into:

1. conditions in which central respiratory drive is increased ('air hunger')
2. conditions where there is an increased respiratory load ('increased work of breathing') or
3. conditions where there is lung irritation ('chest tightness', 'constriction').[23,24]

Keeping these three broad causes in mind will help make the common pathways easier to understand.

Common pathways

MECHANICAL LOADING, RESPIRATORY EFFORT AND 'COROLLARY DISCHARGE'

At times of increased respiratory load or effort, there is a conscious awareness of the activation of the muscles needed to breathe. This sense of effort arises from the brainstem and increases whenever the brainstem signals to increase muscle effort, when the breathing load increases or when muscles are weakened, fatigued or paralysed.[23,24]

In other words, when the CNS voluntarily sends a signal to the respiratory muscles to increase the work of breathing, it also sends a copy to the sensory cortex telling it there is an increased work of breathing. This phenomenon is called 'corollary discharge'.[23]

CHEMORECEPTORS

It has been shown that hypercapnia makes an independent contribution to the experience of breathlessness.[25,26] It is thought that hypercapnia may directly be sensed as 'air hunger', regardless of ventilatory drive.

Hypercapnia also leads to increased brainstem ventilatory output or 'drive' (to

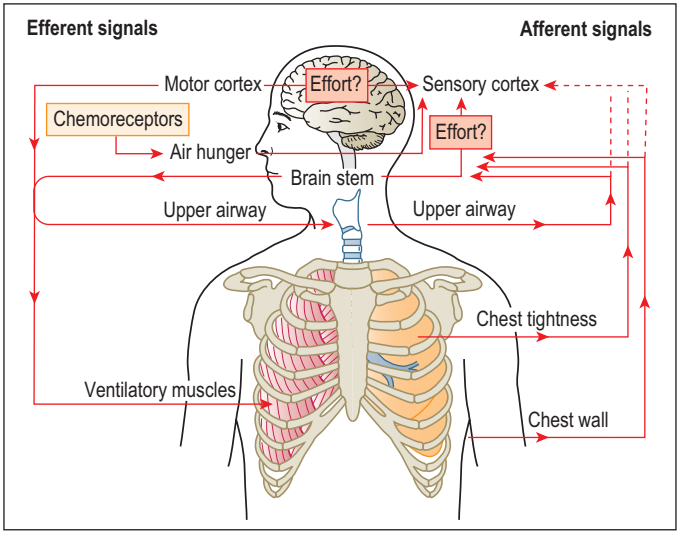

FIGURE 2.6 Mechanisms involved in the sensation of dyspnoea

Based on Manning HL, Schwartzstein RM, N Engl J Med 1995; 333(23): 1547–1553.

blow off the excess carbon dioxide) and this leads to a 'corollary discharge' (discussed above).

Hypoxaemia also contributes to increased ventilation and respiratory discomfort although it has a lesser role than hypercapnia. It is unclear whether hypoxaemia causes dyspnoea directly or via increasing ventilation that is then sensed as dyspnoea.

WHICH CHEMORECEPTORS DO WHAT AND WHERE ARE THEY?

Peripheral chemoreceptors

- Located in carotid and aortic bodies
- Respond to pO_2, increased pCO_2 and H^+ ions

Central chemoreceptors

- Located in medulla
- Sensitive to pCO_2 **not** pO_2
- Respond to changes in pH of cerebrospinal fluid (CSF)

MECHANORECEPTORS

- Upper airway receptors. The face and upper airway have receptors (many of which are innervated by the trigeminal nerve) that can modulate dyspnoea. Mechanoreceptors in the upper airway have been shown to excite or inhibit expiratory and inspiratory muscles and modulate the intensity of dyspnoea.[23]
- Pulmonary receptors. The lung has three types of receptors (slowly adapting receptors, rapidly adapting receptors (RARs) and C-fibres) that transmit information back to the brainstem and brain regarding tension of the airways, lung volume and the state of the lung. These receptors can be stimulated by mechanical or chemical states. Information they detect is transmitted by the vagus nerve (CNX) back to the CNS where, depending on the stimulus, it may be perceived as irritation, chest tightness, air hunger or increased work of breathing.
- Chest wall receptors. Muscle spindles and Golgi apparatus in the muscles of the chest wall function as stretch receptors and monitor 'force generation' and can detect reduced chest wall expansion, thereby contributing to dyspnoea.

NEUROCHEMICAL DISSOCIATION

This refers to a situation where a sudden increased load against respiration occurs but without a compensatory rise in ventilatory effort to overcome the increased load. If this occurs it has been shown to increase dyspnoea.[23]

DECONDITIONING

Deconditioning lowers the threshold at which the muscles used in respiration produce lactic acidosis, causing increased respiratory neural output to reduce carbon dioxide levels.

COPD

Many factors contribute to dyspnoea in COPD.

- Hypoxaemia may stimulate peripheral chemoreceptors, increasing ventilatory drive from the brainstem.
- Hypercapnia may directly cause 'air hunger' but also increased central ventilatory drive (to blow off carbon dioxide) and corollary discharge, as discussed above.
- Increased airways resistance and hyperinflation increases the load that the respiratory muscles must work against, thereby stimulating muscle receptors.
- Deconditioning via increased lactic acidosis may further contribute to dyspnoea.

Anaemia

It is still unclear what causes dyspnoea in anaemia. It is suspected that, in response to reduced blood oxygen levels, the body 'produces' tachycardia, leading to increased left ventricular end-diastolic pressure. This raised pressure then backs up to the lungs and produces an interstitial oedema that reduces lung compliance and stimulates pulmonary receptors.[27]

Alternatively, it has been suggested that a lack of oxygen produces localised metabolic acidosis and stimulation of 'ergoreceptors' (afferent receptors sensitive to the metabolic effects of muscular work).[28,29]

Heart failure

Heart failure may cause dyspnoea via two mechanisms: hypoxaemia or interstitial oedema, stimulating pulmonary receptors (C-fibres). The second cause (interstitial oedema) is the main mechanism. Interstitial fluid decreases lung compliance (which is picked up by pulmonary

C-fibres) and increases the work of breathing.

Asthma

Although not completely understood, the mechanism of dyspnoea in asthma is thought to be related to an increased *sense of effort and stimulation of irritant airway receptors in the lungs*.[24]

- Bronchoconstriction and airway oedema increase the work of breathing and hence the sensation of effort.
- If hyperinflation occurs, this may change the shape of the diaphragm and affect the stretch of the inspiratory muscles, making contraction less efficient and increasing mechanical load. This may lead to increased respiratory motor output and an increased sense of effort.[23]
- Irritation of airway receptors is transmitted by the vagal nerve to the CNS and perceived as chest tightness or constriction.[24]

Neuromuscular disorders

In neuromuscular disorders, central output stimulating respiration is normal; however, muscular strength is often diminished and/or the nerves stimulating the muscles may be weak or damaged. Therefore, additional central neural drive is required to activate the weakened muscles[23] and is sensed as increased respiratory effort and, hence, dyspnoea.

SIGN VALUE

Although a non-specific finding in isolation, dyspnoea at rest does require investigation. Dyspnoea is often the most common sign found in patients with chronic cardiac and lung conditions.

Recent studies[30] showed the sensitivity, specificity and positive predictive value of dyspnoea at rest to be 92% (95% CI=90–94%), 19% (95% CI=14–24%) and 79% (95% CI=77–82%), respectively, in patients with heart failure. Patients with dyspnoea at rest were 13% (LR=1.13; 95% CI=1.06–1.20) more likely to have heart failure than those without.

Given the low specificity of dyspnoea, its value as a sign lies in combining it with other clinical signs or symptoms.[24]

Funnel chest (pectus excavatum)

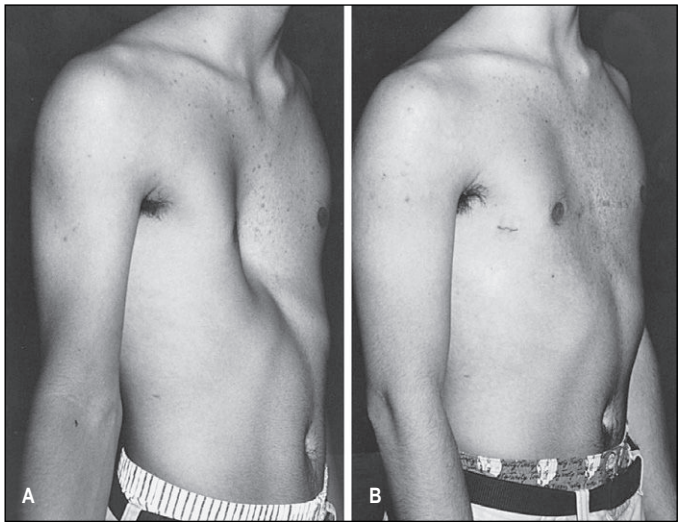

FIGURE 2.7 Funnel chest

A Prior to corrective surgery; **B** post surgery.

Reproduced, with permission, from Shamberger RC, Hendren WH III, Congenital deformities of the chest wall and sternum. In: Pearson FG, Cooper JD et al (eds), *Thoracic Surgery*, 2nd edn, Philadelphia: Churchill Livingstone, 2002: p 1352.

DESCRIPTION

A congenital chest wall deformity where several ribs and the sternum grow abnormally to produce a 'sunken' or concave appearance.

CONDITION/S ASSOCIATED WITH

- Congenital disorder – most common congenital chest wall abnormality
- Congenital diaphragmatic hernia

MECHANISM/S

The mechanism behind the abnormal bone and cartilage growth is not known.

It was initially thought to be due primarily to an overgrowth of cartilage, but recent studies have disputed this.[31] A specific genetic defect has not been identified. 37% of cases have a first-degree relative with the deformity[32] and there is an association with Marfan's syndrome.[33]

Funnel chest was once thought to be partly caused by increased work of breathing during recurrent chest infections in childhood. However, there is no good body of evidence to support this theory at present.

SIGN VALUE

Pectus excavatum can be associated with cardiac malformations and abnormal lung function.

Grunting

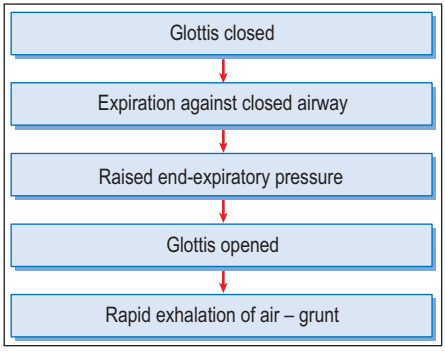

FIGURE 2.8 Mechanism of grunting

DESCRIPTION

A short, explosive, moaning or crying sound heard on expiration, most often in children or neonates.[34]

CONDITION/S ASSOCIATED WITH

Any cause of respiratory distress including, but not limited to:

More common

- Paediatric
  - Respiratory distress syndrome (hyaline membrane disease) – most common cause
  - Meconium aspiration
  - Pneumonia
  - Congestive heart failure

Less common

- Sepsis
- Heart failure

MECHANISM/S

In patients with intrathoracic disease and lower respiratory tract involvement, obstruction or collapse, grunting represents an attempt to increase the functional residual capacity.

The patient forcibly expires against a closed glottis and, in doing so, raises end-expiratory pressure. This helps keep narrowed or collapsing airways open, creating a longer time period for the exchange of oxygen and carbon dioxide at the alveoli.[35] The grunt is caused by the explosive flow of air that occurs when the glottis opens.

SIGN VALUE

Grunting is a very valuable sign associated with severe respiratory distress and requires immediate attention.

Haemoptysis

DESCRIPTION

Coughing or spitting up of blood originating from the lungs or bronchial tubes.[36]

CONDITION/S ASSOCIATED WITH

There are many potential reasons for haemoptysis. Causes include, but are not limited to, the following.

More common

- Infection – bronchitis, pneumonia, tuberculosis
- Cancer
- Pulmonary embolism
- Foreign body
- Airway trauma
- Idiopathic
- Pulmonary venous hypertension

Less common

- Hereditary haemorrhagic telangiectasia
- Coagulopathy
- Wegener's granulomatosis
- Goodpasture's syndrome

MECHANISM/S

The common pathway to haemoptysis is disruption and damage to vascular systems.

Cancer

Neoplasms produce haemoptysis via invasion of superficial mucosa and erosion into blood vessels. It can also be due to a highly vascular tumour with fragile vessel walls.[36]

Pulmonary venous hypertension

Any condition that results in pulmonary venous hypertension may cause haemoptysis. For example, left ventricular failure can lead to increasingly high pulmonary venous pressures. These high pressures damage venous walls, causing blood excursion into the lung and eventually haemoptysis.

Infection

Inflammation of lung tissue may cause disruption of arterial and venous structures. Further repetitive cough can also damage the pulmonary vasculature, leading to haemoptysis.

SIGN VALUE

Although not specific to any one disorder, and bearing in mind that it must be clinically distinguished from haematemesis and other nasal or oral sources of bleeding, haemoptysis always requires investigation.

Harrison's sulcus (also Harrison's groove)

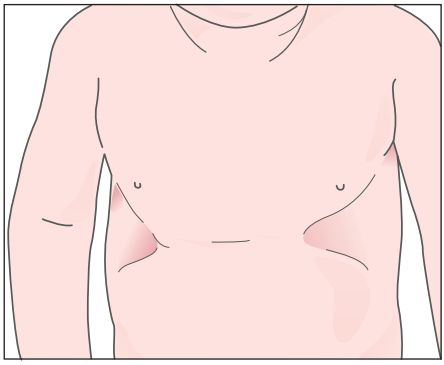

FIGURE 2.9 Harrison's sulcus

Image kindly supplied by Dr Cass Byrnes, Paediatric Respiratory Specialist, The University of Auckland.

DESCRIPTION

The sign shown in Figure 2.9 demonstrates a visible depression of the lower ribs, above the costal margin at the area of attachment of the diaphragm.

CONDITION/S ASSOCIATED WITH

- Rickets
- Severe asthma in childhood
- Cystic fibrosis
- Pulmonary fibrosis

MECHANISM/S

Rickets is a bone disease specific to children and adolescents in which growing bones lack the mineralised calcium required for them to strengthen and harden properly (i.e. the osteoid is not appropriately calcified). Because of this, when the diaphragm exerts downward tension on the weakened ribs, it pulls the bones inward, creating a flared appearance.

Similarly, if a child experiences chronic severe respiratory disease such as asthma before the bones mineralise and harden, the downward tension from the diaphragm and other accessory muscles used during increased respiratory effort can bend the ribs inward over time.

Hoover's sign

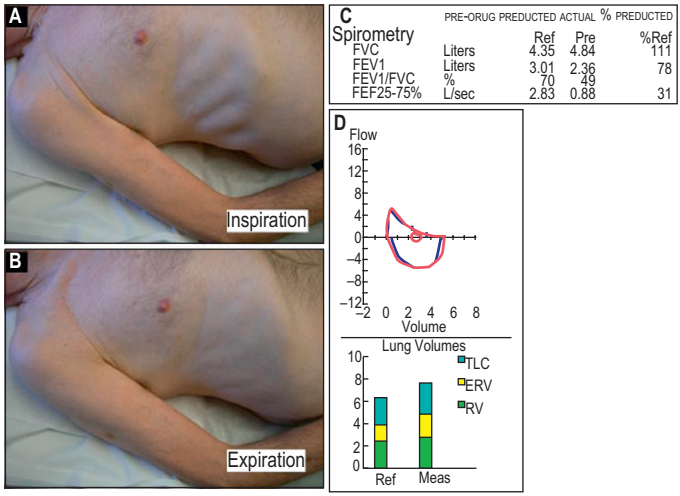

FIGURE 2.10 Hoover's sign

Note the paradoxical inspiratory retraction of the rib cage and lower intercostal interspaces on inspiration.

Based on Johnston C, Krishnaswamy N, Krishnaswamy G, *Clin Mol Allergy* 2008; 6: 8.

DESCRIPTION

The paradoxical inward movement of the lower lateral costal margins on inspiration.

CONDITION/S ASSOCIATED WITH

- Emphysema
- Chest hyperinflation

MECHANISM/S

When the chest becomes severely hyperinflated, the diaphragm often becomes stretched. As a consequence, contraction of the diaphragm at inspiration results in an inward movement,[37] bringing the costal margins with it, as opposed to normal downward movement.

SIGN VALUE

An almost forgotten sign, Hoover's sign was once reported in 77% of patients with obstructive airways disease.[38] A small, more recent study[39] found sensitivity of 58%, specificity of 86% and a PLR of 4.16 – higher than for other signs used in the detection of obstructive airways disease. Hoover's sign is also correlated with more severe obstructive airways disease.

Hypertrophic pulmonary osteoarthropathy (HPOA)

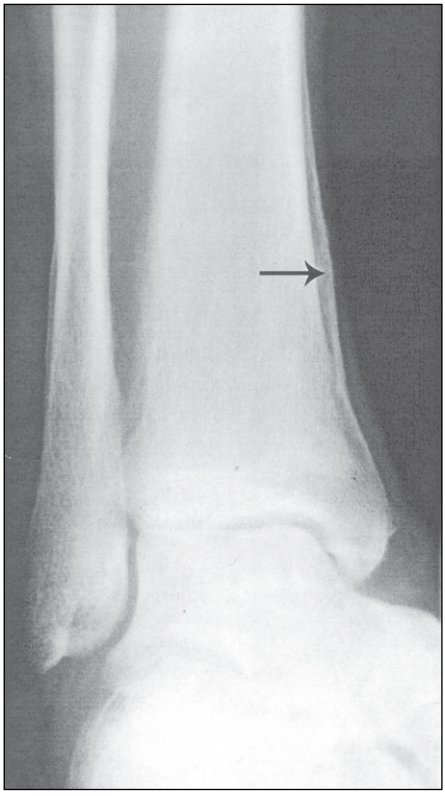

FIGURE 2.11 Hypertrophic pulmonary osteoarthropathy (HPOA)

Reproduced, with permission, from eMedicine; Goldman L, Ausiello D, *Cecil Medicine*, 23rd edn, Philadelphia: Saunders, 2007: Fig 189-2.

DESCRIPTION

A syndrome characterised by excessive proliferation of the skin and bone at distal parts of the extremities, which can include clubbing.[40] In advanced stages of HPOA, periosteal proliferation of tubular bones and synovial effusions can be seen.

CONDITION/S ASSOCIATED WITH

As for clubbing, there are numerous potential causes of HPOA.

More common

- Cyanotic heart disease
- Lung cancer – most often bronchogenic or pleural (metastatic lung cancer is a rare cause)

Less common

- Inflammatory bowel disease
- Infective endocarditis

MECHANISM/S

Clubbing and HPOA are thought to share a common pathogenesis. For a full description of the clubbing mechanism see 'Clubbing' in Chapter 3, 'Cardiovascular signs'.

It is currently postulated that large platelets or megakaryocytes gain access to the peripheral systemic circulation, rather than being broken down within the lung. Once in the extremities, they react with endothelial cells to release a variety of factors including platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF). This results in vascular hyperplasia and proliferation of periosteal layers.[40,41]

Lung cancer

In lung cancer, studies have shown an increased amount of circulating VEGF [42,43] and VEGF deposition in clubbed digits. VEGF is known to produce angiogenesis and proliferation.

SIGN VALUE

HPOA is pathological and investigation as to the cause is warranted, remembering it is not specific to one condition. For the value of clubbing as a sign refer to 'Clubbing' in Chapter 3, 'Cardiovascular signs'.

Hyperventilation

DESCRIPTION

Breathing that occurs in excess of metabolic requirements,[44] usually with an associated tachypnoea.

CONDITION/S ASSOCIATED WITH

There are many causes of hyperventilation. They can be broken down into three main categories:

- Psychiatric
  - Anxiety
  - Panic attacks
- Organic
  - Asthma
  - Pneumonia
  - Bronchiectasis
  - COPD
  - Fibrosing alveolitis
  - Pulmonary embolus
  - Pain
- Physiological
  - Metabolic acidosis
  - Speech
  - Pregnancy

MECHANISM/S

There are various psychological and physical factors that may induce hyperventilation. Figure 2.12 (courtesy of Gardner)[44] demonstrates the different factors at play. The student or junior doctor would not be expected to understand the mechanisms for all aetiologies of hyperventilation; however, there are some key causes and factors worth knowing.

Psychiatric

Hyperventilation may induce (as well as be induced by) feelings of anxiety. In patients with anxiety disorders, there is a predisposition to 'over-breathe' based on biological vulnerability, personality and cognitive variables.[45] For example, anxious patients may interpret non-specific chest pain as a 'heart attack', causing them to attach increased importance to the pain, stimulate the sympathetic nervous system and induce tachypnoeas and hyperventilation. There is also evidence that these patients may have increased chemoreceptor sensitivity to carbon dioxide and, therefore, are more likely to over-breathe in response to a minor increase in carbon dioxide levels.

In panic disorders, the mechanism is unclear. As for anxiety, hyperventilation may induce a panic attack and a panic attack may induce hyperventilation. It is possible that there is a misinterpretation of physiological variables, leading to the brain believing suffocation is taking place and, therefore, inducing inappropriate hyperventilation as a response.[46]

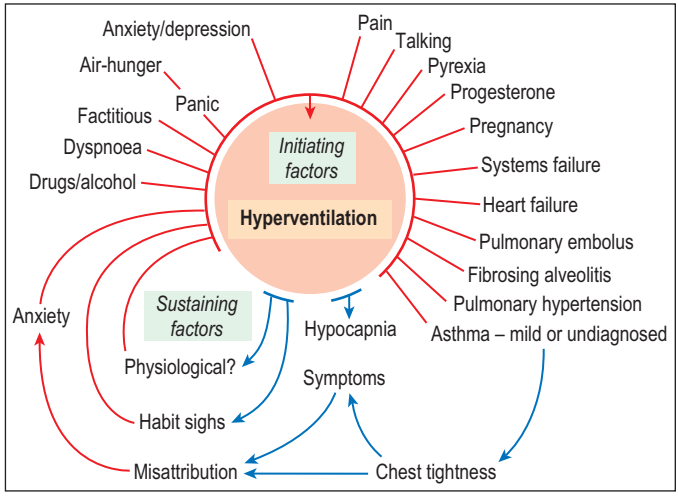

FIGURE 2.12 Factors involved in hyperventilation

Based on Gardner WN, Chest 1996; 109: 516–534.

Organic causes

RESPIRATORY DISEASE

The best researched example is asthma and, even so, the mechanism is inexact. Suggested contributing mechanism/s include:

- hypoxia stimulating hyperventilation via chemoreceptors
- hyperinflation causing stimulation of pulmonary receptors
- misinterpretation of symptoms – having a heart attack leading to a sympathetic response, tachypnoeas and hyperventilation (similar to anxiety).

PULMONARY EMBOLISM

In pulmonary embolism, the primary mechanism of hyperventilation is thought to be hypoxic drive via chemoreceptors.

CNS DISORDERS

Brainstem injuries may cause altered breathing patterns (see 'Ataxic breathing' and 'Apneustic breathing' in this chapter and 'Cheyne–Stokes breathing' in Chapter 3), most likely due to damage to the ventilatory centres. Hyperventilation has been associated with lesions in the pons, medulla and midbrain.

Physiological causes

METABOLIC ACIDOSIS

Metabolic acidosis is a well known cause of tachypnoea as the body attempts to 'blow off' carbon dioxide to reduce acidosis. It is an appropriate response to metabolic requirements and could therefore be argued, by definition, not actually to be hyperventilation.

PREGNANCY

During pregnancy, raised circulating progesterone combines with oestrogen to increase sensitivity to hypoxia, inducing increased ventilation by acting centrally and via the carotid body.[47]

Intercostal recession

DESCRIPTION

This refers to the indrawn skin and soft tissue that can be seen in the intercostal spaces on inspiration during times of respiratory distress.

CONDITION/S ASSOCIATED WITH

Any form of respiratory distress including, but not limited to:

Common

- Hyaline membrane disease
- Pneumonia
- Bronchiolitis
- Anaphylaxis
- Croup
- Epiglottitis
- Foreign body inhalation

MECHANISM/S

In times of increased respiratory effort or respiratory distress, there is increasingly negative intrathoracic pressure, causing the pulling in of skin and soft tissues.

At times of respiratory distress and airway obstruction, the accessory muscles are in use and there is a further decrease in intrathoracic pressure above that which is seen in normal inspiration. This decreased pressure 'sucks' skin and soft tissue inward on inspiration, causing intercostal recession.

SIGN VALUE

Like accessory muscle usage, it is a non-specific sign of increased work of breathing.

Kussmaul's breathing

DESCRIPTION

Also described as 'air hunger', Kussmaul's breathing is typified by deep, rapid inspirations.

CONDITION/S ASSOCIATED WITH

Potentially any cause of metabolic acidosis.

More common

- Diabetic ketoacidosis
- Sepsis
- Lactic acidosis

Less common

- Severe haemorrhage
- Uraemia/renal failure
- Renal tubule acidosis (RTA)
- Salicylate poisoning
- Ethylene glycol poisoning
- Biliary/pancreatic fistulas
- Diarrhoea

MECHANISM/S

Kussmaul's breathing is an adaptive response to metabolic acidosis. By producing deep, rapid inspirations, anatomical dead space is minimised, allowing for more efficient 'blowing off' of carbon dioxide, thus decreasing acidosis and increasing pH.

SIGN VALUE

Although only a few studies have assessed the evidence base for Kussmaul's respiration, it is generally accepted that it is a useful sign. In children, an abnormal respiratory pattern like Kussmaul's respiration has been shown to be a very good sign of 5% or greater dehydration with a likelihood ratio of 2.0.[48]

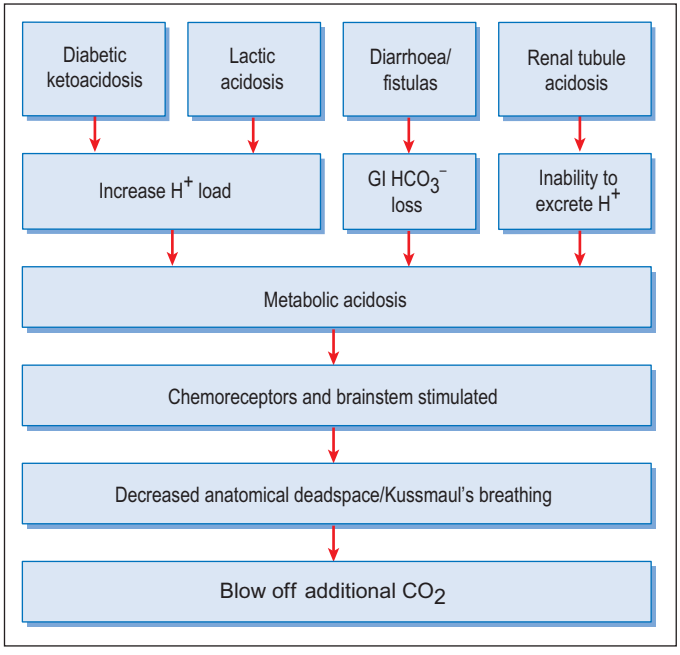

FIGURE 2.13 Kussmaul's respiration mechanism

Orthopnoea

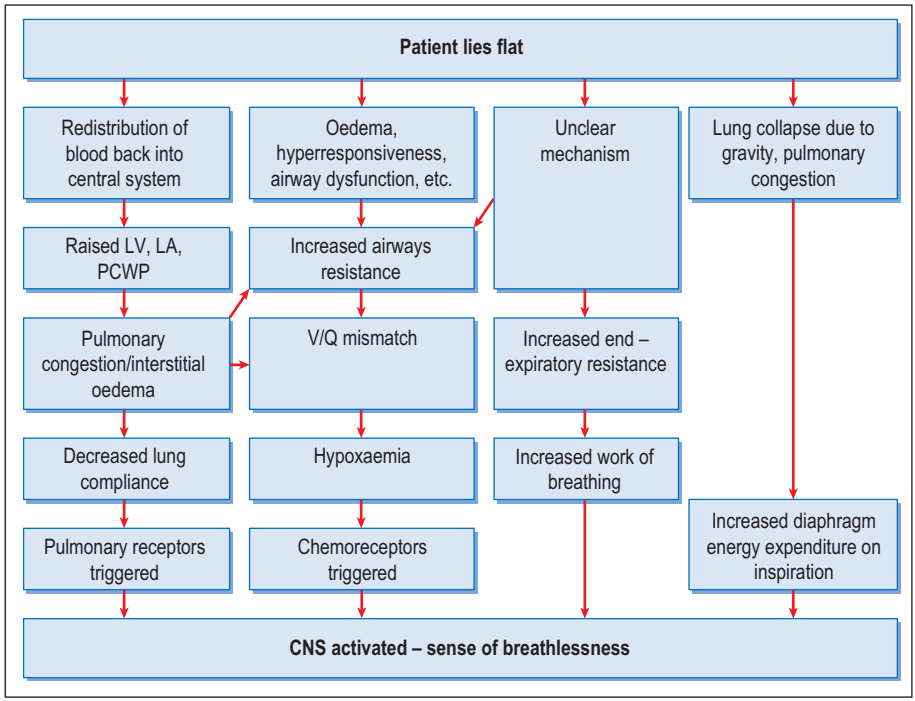

FIGURE 2.14 Mechanism of orthopnoea

DESCRIPTION

Dyspnoea that is made worse by lying in a supine position.

Although more often described as a symptom, with sleep studies becoming a more common occurrence, orthopnoea is increasingly being clinically observed. In either case, it is a useful discovery as the mechanism behind orthopnoea can assist in understanding the underlying condition.

CONDITION/S ASSOCIATED WITH

- Congestive heart failure (CHF)
- COPD
- Asthma

CONGESTIVE HEART FAILURE MECHANISM/S

Despite the fact that orthopnoea has been described in medicine for many years, the reason why it occurs is still not absolutely clear. Figure 2.14 summarises the theories put forward so far.

The current accepted theory for the triggering of orthopnoea is *the redistribution of fluid from the splanchnic circulation and lower extremities into the central circulation that occurs while lying flat.*[49]

In patients with impaired left ventricular function, the additional blood volume that is returned to the heart cannot be pumped out efficiently. Left ventricular, left atrial and, eventually, pulmonary capillary wedge pressure rises, resulting in pulmonary oedema, increased airways resistance, reduced lung compliance, stimulation of pulmonary receptors and, ultimately, dyspnoea.

Furthermore, replacement of air in the lungs with blood or interstitial fluid can cause a reduction of vital capacity, restrictive physiology and air trapping as a result of small airways closure.[49]

Alterations in the distribution of ventilation and perfusion result in relative V/Q mismatch, with consequent widening of the alveolar–arterial oxygen

gradient, hypoxaemia and increased dead space.

Oedema of the bronchial walls can lead to small airways obstruction and produce wheezing ('cardiac asthma').[49]

Recent studies have found additional factors that may contribute to orthopnoea in CHF patients:

- *Increased airflow resistance.* Studies have shown that airflow resistance is increased in patients with CHF when lying supine.[50] The reason for this is still unclear. It may be due to increased airway hyper-responsiveness and/or airway dysfunction, bronchial mucosal swelling, thickening of the bronchial wall, peri-bronchial swelling and increased bronchial vein volume[51] and loss of lung expansion forces due to loss of lung volume.
- *Increased expiratory flow limitation.* There is an increase in expiratory flow limitation in patients with CHF and this is aggravated when they lie flat,[51] making it more difficult for them to expel air from their lungs. Again, the cause of this is not clear. It is possible that when patients lie flat they lose more lung volume (as gravity collapses the lung), further impeding the ability to inspire and expire effectively. Another explanation is that blood redistributing in the lungs affects lung mechanics and increases the expiratory flow limitation.
- *Increased diaphragmatic energy expenditure.*[52] In patients with CHF who are lying flat, there appears to be a rise in diaphragmatic energy expenditure to help deal with the rise in resistive loads to the lung (which the inspiratory muscles must overcome). This increase in the work of the diaphragm also leads to dyspnoea.

SIGN VALUE

Orthopnoea is a valuable sign and relatively specific for CHF. Studies have shown a sensitivity of 37.6% and specificity 89.8%, positive predictive value (PPV) of 15.3% and negative predictive value (NPV) of 96.7%.[53] As in paroxysmal nocturnal dyspnoea (PND), if the sign is absent, it is useful in excluding heart failure as a cause of breathlessness.

Paradoxical abdominal movements (also abdominal paradox)

DESCRIPTION

During normal inspiration, the diaphragm descends and the anterior abdominal wall will move outwards. For paradoxical abdominal movements to be present, the anterior abdominal wall must move outwards with expiration and move inwards on inspiration.[54,55]

CONDITION/S ASSOCIATED WITH

- Neuromuscular disease – bilateral diaphragm weakness
- Diaphragmatic paralysis
- Diaphragmatic fatigue

MECHANISM/S

When the diaphragm is paralysed or not functioning properly, the chest wall and intercostal muscles assume responsibility for breathing. *The movement of the chest wall on inspiration (i.e. outwards) draws the diaphragm and abdominal contents upwards, makes the abdominal cavity pressure more negative and pulls the abdominal wall in.*[8] The weight of the abdominal contents contributes by pushing the diaphragm upwards.

SIGN VALUE

Paradoxical abdominal movements are nearly always pathological and should be investigated immediately.

Paradoxical respiration/breathing

DESCRIPTION

Paradoxical breathing means the deflation of a lung, or a portion of a lung, during the phase of inspiration and the inflation of the lung during the phase of expiration. It may appear simply as inward movement of the chest on inspiration, instead of the normal outward expansion.

CONDITION/S ASSOCIATED WITH

Any cause of respiratory distress:

- COPD
- Pneumonia
- Airway obstruction
- Diaphragm paralysis
- Flail chest

MECHANISM/S

As the diaphragm tires, the accessory muscles assume a larger role in breathing. In an effort to overcome airway obstruction, the accessory muscles produce greater negative intrathoracic pressure on inspiration. This negative pressure sucks the chest inward on inspiration (particularly in children with compliant chest walls).

In addition, this negative pressure may suck the diaphragm upwards, causing the abdomen to move inwards instead of out on inspiration (see 'Paradoxical abdominal movements' in this chapter).

SIGN VALUE

Paradoxical respiration is a sign of severe respiratory distress and as such it is valuable and requires immediate attention and management.

Paroxysmal nocturnal dyspnoea (PND)

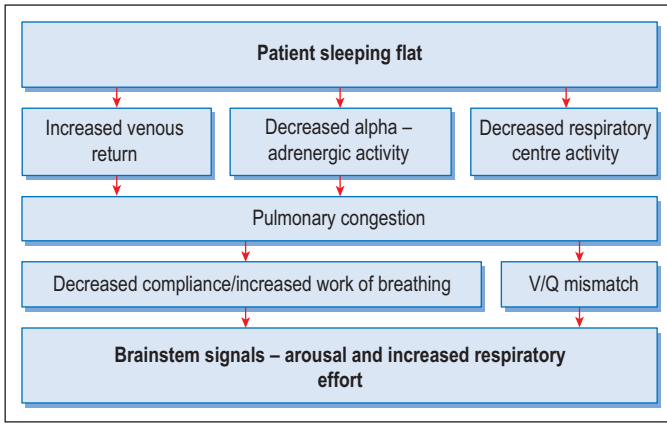

FIGURE 2.15 Mechanism of paroxysmal nocturnal dyspnoea

DESCRIPTION

PND is described as a sudden onset of breathlessness and respiratory distress occurring during sleep (and therefore usually at night). It may also manifest itself as coughing and wheezing fits. Classically described as a symptom, the phenomenon can be observed by clinicians in the hospital setting and its mechanism is often discussed.

CONDITION/S ASSOCIATED WITH

- Congestive heart failure (CHF)

MECHANISM/S

Similar to orthopnoea, the complete mechanism has not been clearly proven. It is thought that PND occurs due to a combination of:

- Increased venous return from the peripheries.
- Reduced adrenergic support of ventricular function that occurs during sleep – leading to the inability of the left ventricle to cope with the increased venous return. This leads to pulmonary congestion, oedema and increased airways resistance.
- Normal nocturnal depression of the respiratory centre.[49]
- Increased pressure in the bronchial arteries, leading to airway compression.[56]

These factors then cause decreased compliance of the lung, increased work of breathing, and prompting of the pulmonary or chest wall receptors, which then activate brainstem stimulation and arousal from sleep. Alternatively, V/Q mismatch occurs causing a transient hypoxaemia that stimulates the brain to cause wakening to correct the imbalance.

SIGN VALUE

PND is a valuable symptom/sign in assessing a patient for heart failure. With sensitivity of 37%, specificity of 89.8%, PPV of 15.3% and NPV of 96.7%, it is useful in ruling out heart failure if it is absent.[53]

Percussion

The act of percussion itself is obviously not a sign; however, understanding the theory behind percussion will help explain why particular percussion notes, which *are* signs, are heard.

Percussion is traditionally said to produce three sounds:

1. tympany
2. resonance/hyper-resonance
3. dullness.

Different pathologies underlie the singular sounds that result from percussion of the various organs. There are two theoretical mechanisms put forward to explain these sounds – the topographic percussion theory and the cage resonance theory. Anyone other than a respiratory physician would not be expected to know either of them but they can help in understanding what the examiner is trying to achieve when they percuss.

TOPOGRAPHIC PERCUSSION THEORY

The central idea in this theory is that only the physical characteristics of tissues directly underneath the percussion 'strike' control the resonance or dullness heard. The body wall between the organ and percussor does not contribute to the sound produced, and the sound itself represents structures only 4–6 cm underneath the location percussed.[57]

CAGE RESONANCE THEORY

Cage resonance theory states that the percussion sound represents the *'ease' with which the body wall vibrates*, which in turn is influenced by the strength of the percussion blow and the state of the body wall and *underlying organs*, and that disease sites *distant* from the percussion blow can influence the note heard.[57]

Despite enthusiasm for the topographic percussion theory, the available evidence strongly supports cage resonance theory as the most likely mechanism.

Percussion: dullness

DESCRIPTION

On percussion of the chest wall and lung fields, a shorter, dull sound of high frequency is heard.

CONDITION/S ASSOCIATED WITH

- Pleural effusions
- Pneumonia

MECHANISM/S

Pleural fluid dampens the normal resonant sound of the lung fields, providing the characteristic 'stony' dullness.

SIGN VALUE

There is good evidence for comparative percussion (comparing right to left lung fields) in predicting significant pleural effusion (PLR of 18.6, NLR of 0.04).[57,58]

Percussion: resonance/hyper-resonance

DESCRIPTION

Low-pitched hollow sounds traditionally heard over the lungs. Hyper-resonant sounds are louder and lower pitched than resonant sounds.

CONDITION/S ASSOCIATED WITH

- Normal lung fields – resonant
- Pneumothorax – hyper-resonant
- COPD – hyper-resonant

MECHANISM/S

In hyper-resonance, hyperinflated lungs allow better transmission of low frequencies produced by the percussion blow.

SIGN VALUE

Hyper-resonance has been shown to have a PLR of 5.1 in detecting patients with chronic airflow obstruction.[59]

Periodic breathing

DESCRIPTION

Thought to be a variant of Cheyne–Stokes respiration, characterised by regular, recurrent cycles of changing tidal volumes in which the lowest tidal volume is less than half of the maximal tidal volume.[60] It is also seen as part of the spectrum of central sleep apnoea.

CONDITION/S ASSOCIATED WITH

- Stroke
- Subarachnoid haemorrhage
- Congestive heart failure

MECHANISM/S

Thought to result from transient fluctuations or instabilities of an otherwise intact respiratory control system.[61]

Several models have been put forward to account for the described fluctuations, but central to all of them is that the pCO_2 transiently falls below the threshold to stimulate respiratory drive. Full details of the mechanisms underpinning Cheyne–Stokes breathing can be found in Chapter 3, 'Cardiovascular signs'.

In strokes and neurological disorders, *transient disruptions of the ventilatory centres of the brainstem combined with a depressed level of consciousness* are thought to be crucial in the development of this breathing pattern.

SIGN VALUE

Frequently seen in patients with left ventricular heart disease, periodic breathing has been shown to be associated with lower left ventricular ejection fractions, lower cardiac indices,[62] higher capillary wedge pressures[63] and, if present at rest, this form of breathing powerfully predicts mortality.[64]

Periodic breathing may occur in up to 25% of patients with stroke.[60] It has been shown to be present in strokes involving autonomic (insula) and volitional (cingulate cortex, thalamus) respiratory networks.[65]

Pigeon chest (pectus carinatum)

DESCRIPTION

Visible prominence of the chest due to outward bowing of the sternum and costal cartilages.

CONDITION/S ASSOCIATED WITH

More common

- Familial
- Childhood chronic respiratory illness

Less common

- Rickets
- Marfan's syndrome

MECHANISM/S

Repeated contractions of the diaphragm (e.g. infections causing prolonged coughing) while the chest wall is still malleable push pliable bones outwards. Over time this causes an irreversible deformation.

It is also thought that an *overgrowth of cartilage* may cause the chest wall to buckle outwards. However, evidence on this is lacking.

SIGN VALUE

Seen in approximately 1 in 1500 births,[66] it is of limited value as a sign in identifying pathology. However, if seen in the context of respiratory illness or symptoms, there is value in reviewing whether the deformity is contributing.

Platypnoea

DESCRIPTION

This refers to shortness of breath on sitting or standing that is relieved by lying supine. It is the opposite of orthopnoea and is not a common sign.

CONDITION/S ASSOCIATED WITH

- Cardiac (intracardiac shunt)
  - Atrial septal defect (ASD)
  - Patent foramen ovale (PFO)
  - Pneumonectomy

  Usually associated with pulmonary hypertension or raised right atrial (RA) pressure (e.g. constrictive pericarditis, cardiac tamponade).
- Pulmonary (intrapulmonary right-to-left shunts)
  - Hepatopulmonary syndrome
  - Pulmonary diseases
  - COPD
  - Pulmonary embolism
- Upper airway tumour
  - Acute respiratory distress syndrome
- Miscellaneous causes
  - Autonomic neuropathy
  - Acute respiratory distress syndrome (ARDS)

GENERAL MECHANISM/S

In general, *shunting of blood from the venous to the arterial system* causes platypnoea. There are multiple physiological ways for this to occur.[67]

Patent foramen ovale

Platypnoea may occur in patients with an isolated PFO or in a patient with a PFO *and* secondary raised RA pressure.

In patients with platypnoea and PFO, there is a postural redirection of inferior vena cava (IVC) blood flow towards the atrial septum and left atrium.[67] Pulmonary hypertension may contribute to this by increasing left ventricular (LV) and left atrial (LA) pressures, which raise the likelihood of blood shunting across the PFO.

Pneumonectomy

In post-pneumonectomy patients, the right ventricle is less compliant than the left ventricle, raising RV and RA pressures and producing a right-to-left shunt and platypnoea.

Pulmonary

Like cardiac causes, pulmonary causes of platypnoea involve *deoxygenated blood being shunted to the arterial system.*

It is suggested that lung disease may cause changes in lung mechanics, raised alveolar pressures, decreased pulmonary artery pressures leading to pulmonary artery compression and increased respiratory dead space[68] – all of which cause worsened V/Q mismatch and/or intrapulmonary shunts resulting in platypnoea.

Hepatic

Platypnoea in liver disease is caused by intrapulmonary shunting of deoxygenated blood. Why and how this occurs is due to a variety of causes.

Hepatic pulmonary syndrome has been shown to cause a number of changes within the pulmonary system that result in altered normal oxygenation:[67]

- Diffuse intrapulmonary shunts are formed mainly by pre-capillary and capillary vascular dilatations (some arteriovenous anastamoses are seen as well).[69]
- Impaired hypoxic vasoconstriction leads to deoxygenated blood passing through areas of poor gas exchange instead of being redistributed to areas with better ventilation.
- Development or worsening of V/Q mismatch.
- Pleural effusions and diaphragmatic dysfunction.

In addition to these factors it is thought that, while sitting up allows gravity to redistribute blood to the lung bases where there are dilated pre-capillary beds, this also means that less oxygenation of blood occurs, producing hypoxaemia and dyspnoea.

Finally, it has also been shown that patients with hepatopulmonary syndrome have a hyperdynamic circulation and low pulmonary resistance – meaning there is less time for deoxygenated blood to become oxygenated in the lungs.

SIGN VALUE

Platypnoea is a rare but valuable sign; if seen it almost certainly indicates underlying pathology resulting in a shunt of blood from the venous to the arterial system.

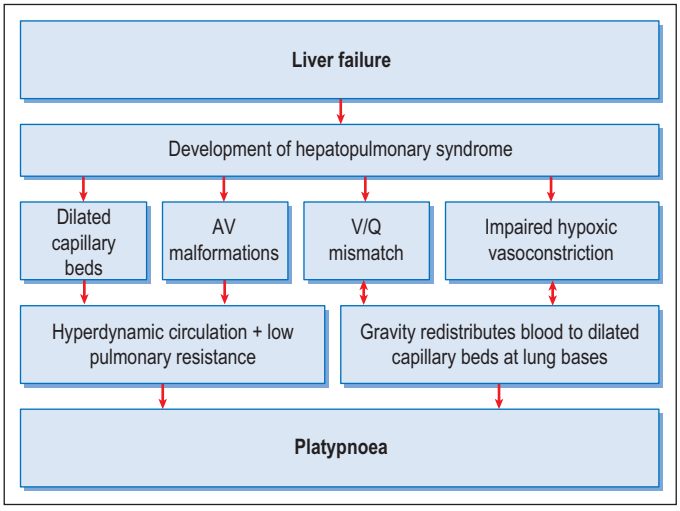

FIGURE 2.16 Mechanism of platypnoea in hepatopulmonary syndrome

Pleural friction rub

DESCRIPTION

Loud rubbing or scratching, crackling sound heard over the lung tissue on auscultation that predominantly occurs in the expiratory phase.

CONDITION/S ASSOCIATED WITH

More common

- Pleurisy
- Lung cancer
- Pneumonia
- Pulmonary embolism

Less common

- Rheumatoid arthritis (RA)
- Systemic lupus erythematosus (SLE)
- Tuberculosis

MECHANISM/S

The common mechanism for a pleural friction rub is *inflammation of the pleura and loss of normal pleural lubrication.*

A local process, such as one caused by infection, embolism or a systemic inflammatory state (as in RA or SLE) may result in inflammation of the pleural lining and the characteristic rub.

POTENTIAL AREAS OF CONFUSION EXPLAINED – PERICARDIAL VERSUS PLEURAL RUBS

Sometimes it may be difficult to decide whether a pleural or pericardial rub is present, especially when some conditions may cause both sounds and both are high-pitched.

- *Pericardial rub.* Often has three distinct sounds – one in systole and two in diastole, which are *independent of respiration*. This rub is more 'distant' in nature and is best heard over the left lower sternal edge.
- *Pleural rub.* Generally composed of two sounds (during inspiration and expiration), this rub is *dependent on respiration* – so the sound will disappear if the patient holds his/her breath. A pleural rub sounds more superficial (i.e. closer to the chest wall).

Pursed lips breathing

DESCRIPTION

Breathing out slowly through the mouth while pursing the lips.

CONDITION/S ASSOCIATED WITH

- COPD

MECHANISM/S

Pursing the lips allows the patient to breathe against resistance, thus maintaining a slow exhalation pressure within the lungs and helping keep bronchioles and small airways open for much-needed oxygen exchange.[70,71] As such, it allows deeper breathing and improved V/Q matching.

SIGN VALUE

Pursed lips breathing has now become a therapeutic modality in patients with COPD to aid in the alleviation of dyspnoea. It has been shown to reduce respiratory rate and increase tidal volume and oxygen saturation.[72,73]

Sputum

DESCRIPTION

Matter/mucus ejected from the lungs, bronchi and trachea through the mouth.

CONDITION/S ASSOCIATED WITH

- COPD
- Pneumonia
- Tuberculosis (TB)
- Bronchiectasis
- Malignancy
- Cystic fibrosis
- Asthma

MECHANISM/S

Mucus is produced by glands within the tracheobronchial tree. Irritants such as cigarette smoke or inflammation increase mucus production. Inflammation and irritation from a variety of causes can stimulate the 'Cough reflex' (see entry in this chapter) to bring up sputum.

SIGN VALUE

A very non-specific sign if produced in isolation from other signs, symptoms or history. However, a recent change in colour or quantity of sputum is worth investigating. Studies have shown:

- Sputum culture samples are of limited value in COPD unless infection is not responding to antibiotics.[74]
- In patients with COPD, the presence of green (purulent) sputum was 94.4% sensitive and 77.0% specific for the yield of a high bacterial load, making it useful in identifying patients who need antibiotics.[61]
- In patients with white-, cream- or clear-coloured sputum, bacterial count was low and further testing was not warranted.[75]
- In Australian COPDX guidelines, an increased volume and/or change of colour of sputum is used as a marker for an exacerbation of COPD.
- There is debate over the value of sputum and sputum gram stain and cultures in community-acquired pneumonia.[76] A recent study[77] found sputum gram stain is a dependable diagnostic test for the early aetiological diagnosis of bacterial community-acquired pneumonia that helps in choosing rational and appropriate initial antimicrobial therapy. However, there is a cost to the test and, given that most CAPs are caused by streptococcal pneumonia, it maybe prudent to treat empirically and only test high-risk or difficult-to-treat cases.
- In TB endemic areas, sputum collection is a key tool in the diagnosis and management of TB. The diagnostic value of 'rust-coloured' sputum in TB is not clear. Microscopic examination is needed.

Stertor

DESCRIPTION

A form of noisy breathing described as a snoring sound easily heard at the bedside. Unlike stridor, stertor does not have a musical quality and is low-pitched. It is the type of breathing usually associated with congestion and nasal 'stuffiness' and usually originates at the level of naso/oropharynx. It is most often heard in, and associated with, paediatric patients, especially infants.

CONDITION/S ASSOCIATED WITH

- Typically, nasopharyngeal and oropharyngeal obstruction
- Nasal obstruction and deformity
- Adenoid hypertrophy
- Epiglottitis
- Glioma (if blocking nasal passage)

MECHANISM/S

Stertor is caused by airway narrowing causing airflow turbulence, usually due to an oropharyngeal obstruction.

Stridor

DESCRIPTION

Stridor is a loud, intense, monophasic sound with constant pitch. It is best heard over the extrathoracic airways and maybe inspiratory, expiratory or biphasic in timing.

CONDITION/S ASSOCIATED WITH

Any form of upper airway obstruction.

More common

- Foreign body
- Croup
- Peritonsillar abscess
- Aspiration

Less common

- Laryngomalacia – chronic low-pitched stridor, most common form of inspiratory stridor in neonates
- Subglottic stenosis – chronic, common form of biphasic
- Vocal cord dysfunction – chronic, common form of biphasic
- Laryngeal haemangiomas
- Tracheomalacia and bronchiomalacia – expiratory stridor
- Epiglottitis

MECHANISM/S

Any obstruction in the extrathoracic (supraglottis, glottis, subglottis and/or trachea) airways causes *narrowing and turbulence to flow*, producing the sound (Table 2.2).

On inspiration, the negative pressure within the airways narrows the area of obstruction further, often making stridor more marked.

Characteristics of stridor

The volume, pitch and phase of stridor can be useful in localising the obstruction.[78]

- *Volume:* stridor is believed to represent a significant narrowing of the airway[78] but a sudden drop in volume may indicate impending airway collapse.[79]
- *Pitch*
  - High-pitched stridor is usually caused by obstruction at the level of the glottis.[80]
  - Lower-pitched stridor is often caused by higher lesions occurring in the nose, nasopharynx and supraglottic larynx.[81]
  - Intermediate pitch usually signifies obstruction at the subglottis or below.[81]
- Phase
  - Inspiratory – the obstruction is usually above the glottis.[82]
  - Biphasic – fixed obstruction at the glottis or subglottis down to tracheal ring.[78]
  - Expiratory – suggests collapse of the lower airways below the thoracic inlet.[78]

SIGN VALUE

Stridor is a valuable sign in identifying upper airways obstruction and once heard is never forgotten. It must be investigated and managed quickly.

TABLE 2.2 Type of stridor and location of obstruction

Stridor type	Obstruction location
Inspiratory	Laryngeal/supraglottic lesion
Expiratory	Tracheobronchial lesion – below thoracic inlet
Biphasic	Subglottic/glottic to tracheal ring

Subcutaneous emphysema/surgical emphysema

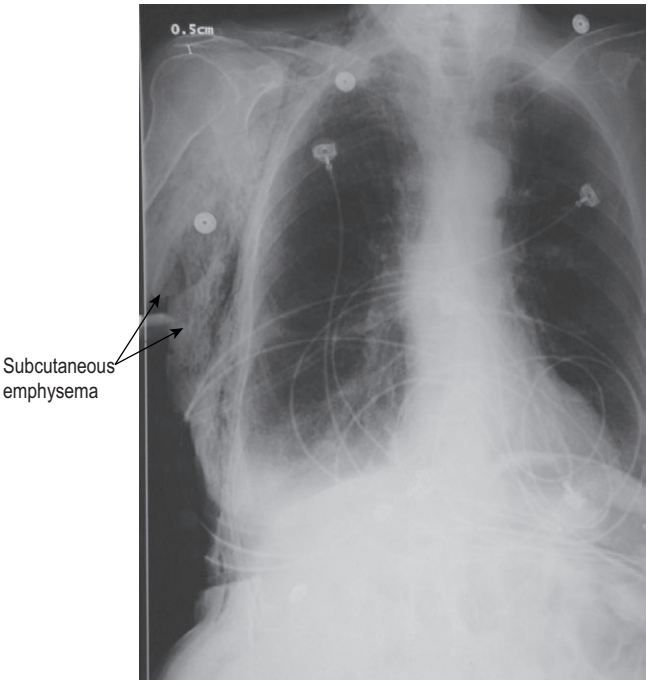

FIGURE 2.17 X-ray of subcutaneous emphysema

Reproduced, with permission, from Roberts JR, Hedges JR, *Clinical Procedures in Emergency Medicine*, 5th edn, Philadelphia: Saunders, 2009: Fig 10-12.

DESCRIPTION

Air or gas within the subcutaneous layer of the skin. On palpation there will be a crackling feeling (like bubble wrap) and there may be obvious changes to the skin texture.

CONDITION/S ASSOCIATED WITH

Blunt or sharp trauma causing puncture of gastrointestinal organs or lungs.

- Pneumothorax
- Pneumomediastinum
- Barotrauma
- Oesophageal rupture

MECHANISM/S

Subcutaneous emphysema is caused by air or gas reaching the subcutaneous layer of the skin.

Skin from the neck, mediastinum and retroperitoneal space is *connected by fascial planes* and it is these planes that allow air to track from one space to another.[83]

Typically, subcutaneous emphysema is caused by sharp or blunt trauma to the lungs. If the lung is punctured (whether at the parietal or visceral pleura), air is able to track up the peri-vascular sheaths, into the mediastinum and from there enter subcutaneous tissues.

Similarly, in barotrauma, excess pressure in the lungs may cause the alveoli to burst and air to travel below the visceral pleura, up to the hilum of the lung, along the trachea and into the neck.

SIGN VALUE

A valuable sign; subcutaneous emphysema in the presence of chest wall trauma usually indicates a more serious thoracic injury involving an air-containing structure of the thorax.[84]

Tachypnoea

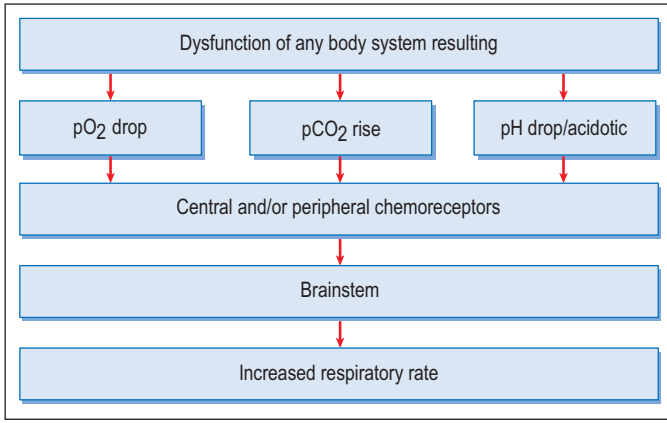

FIGURE 2.18 Simplified mechanism of tachypnoea

DESCRIPTION

A respiratory rate above 20 breaths per minute.

CONDITION/S ASSOCIATED WITH

Tachypnoea may be produced by many different system pathologies including:

- Cardiac
- Respiratory
- CNS
- Infectious
- Psychiatric

MECHANISM/S

Any state causing a derangement in oxygen (hypoxia), pCO_2 (hypercapnia) or acid/base status (acidosis) will stimulate respiratory drive and increase respiratory rate.

Tachypnoea occurs *in most situations as a compensatory response to either a drop in pO_2 (hypoxaemia) or a rise in pCO_2 (hypercapnia)*. Central chemoreceptors in the medulla and peripheral chemoreceptors in the aortic arch and carotid body measure a combination of these variables and send messages to the central ventilatory systems to increase respiratory rate and tidal volume to compensate for any fluctuations.[85]

SIGN VALUE

Tachypnoea is a very valuable sign and is unfortunately often neglected as a vital sign when checking routine observations. Studies reviewing tachypnoea have shown:

- Predicting cardiopulmonary arrest – sensitivity of 0.54, specificity 0.83, odds ratio 5.56.[86]
- In unstable patients, the change in respiratory rate is better at predicting an at-risk patient than heart rate or blood pressure.[87]
- Unwell patients with a higher respiratory rate had a higher risk of death.[88]
- Over half of all patients suffering a serious adverse event on the general wards had a respiratory rate greater than 24 breaths/minute.[89]
- In predicting negative outcomes (ICU admission or death) in community-acquired pneumonia, respiratory rate of greater than 27 had sensitivity of 70%, specificity of 67%, PPV of 27% and NPV of 93%.[85]

Onset of tachypnoea or change in rate of tachypnoea warrants quick and thorough investigation in all patients and may herald ominous decompensation.

Tracheal tug

DESCRIPTION

Downward displacement of the thyroid cartilage during inspiration.

CONDITION/S ASSOCIATED WITH

Most common

- Respiratory distress/COPD (Campbell's sign)

Less common

- Arch of aorta aneurysm (Oliver's sign)

MECHANISM/S

Tracheal tug – Campbell's sign

Patients in respiratory distress have an increased work of breathing where the *movements of the chest walls, muscles and diaphragm* are transmitted along the trachea, pulling it rhythmically downwards.

Tracheal tug – Oliver's sign

Tracheal tug in this instance refers to the downward displacement of the cricoid cartilage with ventricular contraction, in the presence of an aortic arch aneurysm. With the patient's chin lifted, the examiner grasps the cricoid cartilage and pushes it upwards. This movement brings the aortic arch and the aortic aneurysm closer to the left main bronchus (which it overrides). The pulsation of the aorta and the aneurysm is then transmitted up the bronchus to the trachea.

SIGN VALUE

Limited evidence as to value; however, tracheal tug is generally accepted as a sign of increased work of breathing.

Oliver's sign is much rarer than a tracheal tug seen in a patient with COPD and/or respiratory distress.

Trepopnoea

DESCRIPTION

Dyspnoea seen to be worse when the patient is lying on one side (in lateral decubitus position), which is relieved by lying on the opposite side.

CONDITION/S ASSOCIATED WITH

- Unilateral lung disease
- Congestive heart failure – dilated cardiomyopathy
- Lung tumour

MECHANISM/S

Unilateral lung disease

When the patient lies on the side of the good lung, gravity increases blood flow to the lower lung and improves oxygenation.

Congestive heart failure

These patients prefer to lie on their right side. The cause of this preference is as yet unclear.

Recent studies[90] suggest that lying on the right side enhances *venous return and sympathetic activity*. It is also thought that the right lateral position allows changes to the *hydrostatic forces* on the right and left ventricles, which can reduce lung congestion.

Other potential contributing factors include:

- positional improvements in lung mechanics – the enlarged heart is not causing atelectasis by pushing on the lung
- less airway compression.

Lung tumour

Gravity causes tumours to compress the lung or blood vessels, depending on their location. Therefore, a tumour of sufficient size in a significant site can cause a transient V/Q mismatch, hypoxia/hypercarbia and breathlessness.

SIGN VALUE

There is limited evidence on the sensitivity and specificity values; however, trepopnoea is pathological and requires investigation.

Vesicular breath sounds

DESCRIPTION

Often described as quiet, wispy sounds with a short inspiratory phase and very quiet expiratory phase.

CONDITION/S ASSOCIATED WITH

- Normal

MECHANISM/S

Turbulent airflow in larger airways causes the sound. Since other lower-pitched sounds are attenuated by the lung and chest wall[91] in the healthy person, this leaves the higher-pitched vesicular sounds as the only audible noise on auscultation.

Vocal fremitus/tactile fremitus

DESCRIPTION

The vibration felt when placing the hands on the back of a patient and asking them to speak (usually the phrase 'ninety-nine'!). The vibration is decreased in increased areas of air, fat, fluid or tumour, whereas it is increased in areas of consolidation. Symmetrical fremitus may be physiological, whereas asymmetrical fremitus should always be considered abnormal.

CONDITION/S ASSOCIATED WITH

- Pneumonia – increased vocal fremitus
- Pneumothorax – decreased fremitus
- Pleural effusion – decreased fremitus
- COPD – decreased fremitus
- Tumour

MECHANISM/S

As discussed in 'Vocal resonance' in this chapter, variation in vocal fremitus can be explained by the manner in which various *voice frequencies are transmitted through tissue or fluid*.

In pneumonia, consolidation *augments lower frequencies* (e.g. a human's voice) and thus is more likely to be felt as an increase in vocal fremitus. Large pleural effusions decrease the *transmission of low frequencies* – and thus diminish vocal fremitus.

SIGN VALUE

See box under 'Vocal resonance'.

Vocal resonance

DESCRIPTION

Vocal resonance refers to the character of the patient's voice heard with the stethoscope on the back (over the lung fields). Normally a patient's voice is muffled and difficult to understand in this situation but in consolidated areas it will be heard clearly.

Classically, the changes in vocal resonance seen with disease are:

- bronchophony – voice is louder than normal
- pectoriloquy – whispered words are clearly heard, also called 'whispering pectoriloquy'
- aegophony – a nasal, bleating quality to the sound, like a goat. Implies high resonance.

CONDITION/S ASSOCIATED WITH

Changes in vocal resonance are classically associated with:

- Consolidation: tumour, pneumonia
- Pleural effusion

MECHANISM/S

The differences in vocal resonance are determined by the *frequency transmission (Hz)* and physical properties of normal lungs, fluid and consolidation.

Normal lung tissue filters out lower-frequency sounds and transmits high-frequency sounds.[8] Human voices are *generally lower in frequency* and, therefore, are not transmitted well.

Consolidated lungs transmit *low and higher frequencies well* and, therefore, a patient's voice is heard more clearly and easily over a consolidated area.

Large effusions (due to the physical properties of fluid) *reduce the transmission of lower frequencies*[9,92,93] and, therefore, voices are heard muffled or less clearly than normal.

SIGN VALUE

In patients with cough and fever, shown to have a very good specificity for detecting pneumonia – sensitivity of 4–16%, specificity of 96–99%.[9]

VOCAL FREMITUS VERSUS VOCAL RESONANCE

Vocal fremitus and resonance are two much-taught but probably underutilised clinical signs. One study[8] looking at pleural effusions showed the following diagnostic utility.

- *Reduced vocal fremitus*: sensitivity 82%, specificity 86%, PPV 0.59, NPV 0.95, PLR 5.67, NLR 0.21
- *Reduced vocal resonance*: sensitivity 76%, specificity 88%, PPV 0.62, NPV 0.94, PLR 6.49, NLR 0.27

Wheeze

DESCRIPTION

Continual high-pitched 'musical' sounds heard at the end of inspiration or at the start of expiration.

CONDITION/S ASSOCIATED WITH

- Asthma
- Respiratory tract infections
- COPD
- Foreign body aspiration: bronchial foreign bodies in children may present with a 'triad' of unilateral wheeze with cough and decreased breath sounds

MECHANISM/S

Airway narrowing allows airflow-induced oscillation of airway walls, producing acoustic waves.[94] As the airway lumen becomes smaller, the air flow velocity increases, resulting in vibration of the airway wall and the musical tonal quality.

SIGN VALUE

A wheeze on normal quiet expiration or inspiration is most likely pathological. The longer and more high-pitched the wheeze, the more severe the obstruction is.[95] Also remember that having a wheeze implies that the patient has enough air movement to create a wheeze. Beware the wheezing patient who suddenly becomes silent, as this may mean air movement is so *low* that a wheeze cannot be produced. If this occurs, respiratory arrest is imminent.

MONOPHONIC VERSUS POLYPHONIC WHEEZE

Monophonic wheeze

A wheeze with a single note that starts and ends at different points in time. The classic example is a tumour in the bronchi. The pitch and timing is fixed as the tumour is fixed in one location.

A child with a fixed foreign body may have a monophonic wheeze.

Polyphonic wheeze

Several different tones starting and finishing at the same time. Heard when a fixed compression occurs in multiple bronchi at the same time. Normally found in COPD and in normal people at end expiration. It is caused by the second- or third-order bronchi closing at the same time at end expiration, as the pressures within the airway keeping them patent are reduced.

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CHAPTER 3

Cardiovascular Signs

Apex beat (also cardiac impulse)

DESCRIPTION

The normal cardiac impulse or 'apex beat' should be felt in the left fifth intercostal space in the midclavicular line over an area 2–3 cm^2 in diameter.[1]

The normal impulse is described as a brief outward thrust occurring in early systole and will disappear before S2 is heard. It coincides with isovolumetric contraction.

Apex beat: displaced

DESCRIPTION

Normally the apex beat of the heart is palpated in the left fifth intercostal space in the midclavicular line. A 'displaced' apex beat usually implies that the impulse is felt lateral to the midclavicular line or more distally.

CONDITION/S ASSOCIATED WITH

Similar conditions to the pressure- and volume-loaded beats described below.

More common

- Left ventricular enlargement of any cause – apex is usually displaced downwards and laterally
- Right ventricular enlargement of any cause – apex is displaced laterally
- Cardiomyopathies and dilatation of the heart
- Congestive heart failure
- Valvular heart disease

Less common

- Situs inversus/dextrocardia

MECHANISM/S

The displacement of the apex beat is related to physical changes in the heart size, whether via hypertrophy of the muscle (e.g. aortic stenosis and left ventricular hypertrophy) or dilatation of the heart (e.g. dilated cardiomyopathy). With the enlargement or dilatation of the heart (or both), the apex grows or moves laterally/downwards.

SIGN VALUE

If detected, a valuable sign.

One review has indicated that the PLR for left ventricular systolic dysfunction is 16.0 (8.2–30.9)! However, the sign may be detected infrequently so its absence does not rule out systolic dysfunction.[2]

Apex beat: hyperdynamic apical impulse/volume-loaded

DESCRIPTION

On palpation of the praecordium, the apex beat will be diffuse (i.e. over an area greater than 3 cm^2), with a large-amplitude thrust against the hand that quickly disappears.

CONDITION/S ASSOCIATED WITH

Classically associated with states of volume overload and hypermetabolic states.[1,3,4]

More common

- Aortic and mitral regurgitation
- Thyrotoxicosis
- Sympathetic nervous system activation
- Anaemia

Less common

- Patent ductus arteriosus
- Ventricular septal defect

MECHANISM/S

In hyperdynamic states, the impulse felt is simply an exaggeration of the normal cardiac beat.

In *volume-overloaded* states, the Frank–Starling mechanism produces a more forceful ventricular contraction.

SIGN VALUE

The hyperdynamic impulse has been shown to be related to increased left ventricular volume.[5] One study demonstrated that an apical impulse over an area greater than 3 cm had a sensitivity of 92% with 91% specificity for an enlarged ventricle (PPV 86% and NPV 95%).[6]

Apex beat: left ventricular heave/sustained apical impulse/pressure-loaded apex

DESCRIPTION

Used to describe an apex beat that is holosystolic in nature (i.e., that lasts through systole to S2).

CONDITION/S ASSOCIATED WITH

More common

Classically seen in *pressure-loaded* states:

- Hypertension
- Aortic stenosis
- Hypertrophic obstructive cardiomyopathy

Less common

- Dilated heart
- After myocardial infarction

MECHANISM/S

In order to compensate for increased *pressure load* on the left ventricle, the ventricle enlarges in size, making it more likely to be palpable. In conditions of increased afterload, ejection of blood out of the left ventricle is prolonged throughout systole, giving the impression of a sustained impulse through to S2.

SIGN VALUE

Although not extensively researched, a left ventricular heave has been shown in one study to be superior to electrocardiography in predicting left ventricular hypertrophy[7] (sensitivity 88%, specificity 78%).

Arterial pulse

The arterial pulse waveform can be difficult to classify and is an often-neglected clinical sign. The differences between pulse patterns may be subtle and therefore difficult (or impossible) for the expert as well as the novice to detect clinically without intra-arterial monitoring. They are discussed as a group for ease of comparison, and the important clinical pulse forms are highlighted. In order to understand the mechanism/s that create alternative pulse waveforms and the differences between them, a basic revision of the normal arterial waveform and some important definitions are first explained.

KEY CONCEPT EXPLAINED – THE NORMAL ARTERIAL WAVEFORM

Like the jugular venous pulse, the arterial pulse has a waveform, as shown in Figure 3.1. The waveform and arterial pressure are made up of two main components: the *pulse wave* (or pressure wave) and the *wave reflection.*

Pulse wave

The pulse wave is the pressure felt against the finger when palpating a pulse and represents the wave produced by left ventricular contraction.

Wave reflection

The waveform you feel when taking a pulse, which is visible on monitoring, is created by more than just the pulse wave or forward flow of systole. Narrowing and bifurcation of blood vessels cause impedance, which forces the pressure wave to be reflected back on itself, and the systolic blood pressure and waveform to be amplified. The easiest analogy to use is that of waves in the ocean: if one wave travelling in one direction hits another wave heading in the opposite direction, the resulting collision is larger than the two independent waves.[8]

Anacrotic limb or upstroke

The anacrotic or ascending limb of the arterial waveform mainly reflects the pressure pulse produced by left ventricular contraction.[9]

Dicrotic limb and dicrotic notch

The dicrotic or descending limb of the waveform represents the decreasing pressure after left ventricular contraction. The dicrotic notch represents the closure of the aortic valve and retrograde or regurgitant flow across the valve.

IMPORTANT CONCEPT EXPLAINED – THE VENTURI PRINCIPLE

The Venturi principle is central to understanding the mechanism of arterial pulse signs. It states that, when fluid flows through a constricted pipe (in this case a blood vessel), the pressure of the fluid (blood) drops. This causes constriction of the vessel (see Figure 3.2).

The importance of this will be demonstrated in the clinical signs below.

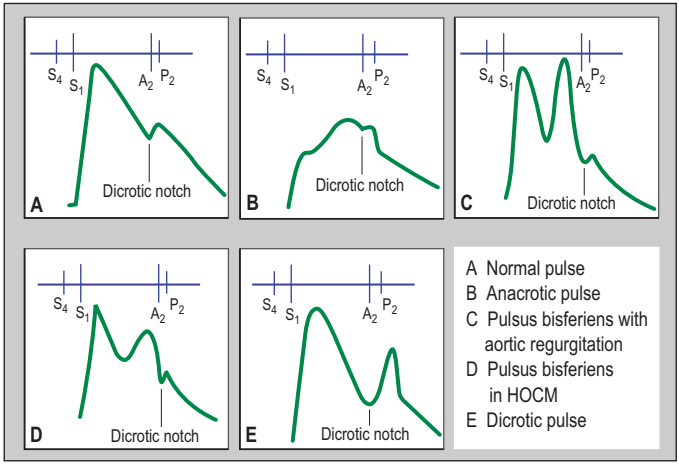

FIGURE 3.1 Configurational changes of the carotid pulse

A Normal pulse; **B** anacrotic pulse; **C** pulsus bisferiens; **D** pulsus bisferiens; **E** dicrotic pulse

Based on Chatterjee K, Bedside evaluation of the heart: the physical examination. In: Chatterjee K et al (eds), *Cardiology. An Illustrated Text/Reference*, Philidelphia: JB Lippincott, 1991: Fig 48.5.

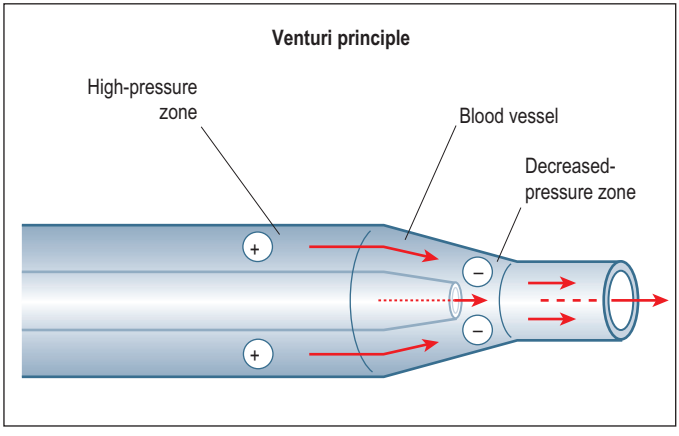

FIGURE 3.2 Schematic representation of the venturi principle

Based on Vender JS, Clemency MV, Oxygen delivery systems, inhalation therapy, and respiratory care. In: Benumof JL [ed], *Clinical Procedures in Anesthesia and Intensive Care*, Philadelphia: JB Lippincott, 1992: Fig 13-3.

Arterial pulse: anacrotic

DESCRIPTION

A slow rising pulse that gives the impression of an interruption of the upstroke of the pulse on the ascending limb of the waveform (see Figure 3.1B). The peak of the limb is closer to the second heart sound.

CONDITION/S ASSOCIATED WITH

- Aortic stenosis

MECHANISM/S

Like pulsus tardus (see 'Pulsus tardus' in this section), the anacrotic pulse of aortic stenosis can be attributed to *prolonged ventricular ejection* and the *Venturi effect in the aorta.*[8] The stenosis or narrowing of the aortic valve means it takes longer to eject blood out of the left ventricle. This longer ejection time delays the upstroke of the pulse so the peak occurs closer to the second heart sound. Valvular narrowing creates a Venturi effect that further reduces the diameter of the arterial lumen, thus giving the feeling of an interrupted upstroke on palpation.

Arterial pulse: bigeminal

DEFINITION

As the name suggests, this is a doubled or twinned pulse (*bi* – 'two' and *geminus* – 'twins'). Two beats of a peripheral pulse occur in rapid succession, followed by a long pause, then another two beats in rapid succession. It is an irregular pulse.

CONDITION/S ASSOCIATED WITH

- Severe heart failure
- Hypovolaemic shock
- Cardiac tamponade
- Sepsis

MECHANISM/S

The bigeminal pulse is created by a normal sinus beat followed by a premature contraction. The premature beat has less stroke volume and, therefore, the strength of the pulse varies between the two beats.

Arterial pulse: dicrotic

DESCRIPTION

In a dicrotic pulse, there are two beats per cardiac cycle, one during systole and the second in diastole. If the patient is being intra-arterially monitored, a dicrotic pulse will produce a characteristic 'M'-shaped waveform (see Figure 3.1).

CONDITION/S ASSOCIATED WITH

Generally seen in younger patients with low cardiac output states and elevated systemic vascular resistance:

- Cardiomyopathy/heart failure[10]
- Post valve replacement surgery[11]
- Sepsis
- Hypovolaemia
- Heart failure

MECHANISM/S

In a dicrotic pulse, there is an accentuated diastolic dicrotic wave after the dicrotic notch (aortic valve closure).

Low stroke volume combined with *intact arterial vascular resistance* must be present for a dicrotic pulse to occur.[11,12]

In patients with a normal arterial pulse (see Figure 3.1), a dicrotic wave (thought to be caused by rebounding of blood against the aortic valve) is measurable on waveform analysis but is too low in amplitude to be felt on palpation and is hidden by the larger normal systolic wave.

In disease states resulting in low stroke volume, the systolic wave is smaller, making it easier to palpate the dicrotic wave. When combined with an intact arterial system (which amplifies the rebound of the pulse during diastole), the dicrotic pulse may be felt.[10–12]

SIGN VALUE

There are few studies reviewing the value of a dicrotic pulse. There is some evidence that a dicrotic pulse noticed after valve surgery carries a worse prognosis;[12] however, the pulse (if felt) is frequently confused with pulsus bisferiens and, therefore, may have limited value as a sign.

Arterial pulse: pulsus alternans

DESCRIPTION

Alternating strong and weak beats.

CONDITION/S ASSOCIATED WITH

- Advanced left ventricular failure[13–17]
- Aortic valve disease

MECHANISM/S

Several mechanisms have been postulated,[12] with two associated with the most evidence:

- Frank–Starling theory – in left ventricular dysfunction there is a decrease in cardiac output that causes a raised end-diastolic volume. This raised volume allows for greater myocardial stretch and, via the Frank–Starling mechanism, causes the next contraction to be more forceful (the strong beat). After the strong beat, the end-diastolic volume is smaller and, hence, the next beat is weaker.
- Inherent beat-to-beat variability – this theory is based on the concept that there is inherent beat-to-beat variability in myocardial contractility, i.e. that the myocardium can vary its inotropic state and, therefore, the force of contraction from one beat to the next.

Other suggested mechanisms include:[13]

- failure of the ventricle to completely relax after a strong beat, causing incomplete filling in diastole
- alternations of preload and afterload
- sympathetic system and baroreceptor influences
- alternations of cardiac action potentials
- variations in intracellular calcium[8,18] – in diastolic left ventricular dysfunction, ejection duration is prolonged due to slowed calcium reuptake.

SIGN VALUE

There are few well conducted studies on the value of pulsus alternans as a sign. However, if present, studies have shown pulsus alternans to have a reasonable correlation with left ventricular dysfunction.[14–17] It is a valuable sign worth seeking in patients suspected of having cardiac dysfunction.

Arterial pulse: pulsus bisferiens

DESCRIPTION

As seen in Figure 3.1D, the 'normal' pulse is characterised by two systolic peaks separated by a mid-systolic dip. Often only the first systolic peak is felt when taking a pulse. The first systolic peak is the percussion wave caused by rapid left ventricular ejection, and the second peak is created by the wave hitting the peripheral vessels and being reflected back.

In pulsus bisferiens, both peaks are accentuated, resulting in *two systolic peaks* of the pulse with a mid-systolic dip being palpable.

CONDITION/S ASSOCIATED WITH

More common

- Aortic regurgitation
- Aortic regurgitation with milder aortic stenosis
- Hypertrophic cardiomyopathy

Less common

- Large patent ductus arteriosus – rare
- Arteriovenous fistula – rare

GENERAL MECHANISM/S

In aortic regurgitation with aortic stenosis, the Venturi effect is responsible for the pulse felt. Rapid blood flow through the aortic valve sucks in the walls of the aorta. This momentarily reduces the flow and produces a notch between the systolic peaks of the arterial waveform.[19–21]

This is the same principle as the mechanism underlying the anacrotic pulse. However, in aortic stenosis the Venturi effect reduces a **normal** amplitude pulse whereas, in the setting of aortic regurgitation, the initial pulse amplitude is **higher**. Due to this higher output state and the additional regurgitant volume being ejected from the ventricle, the first systolic peak of the pulse becomes more obvious (see Figure 3.1D).[8]

Hypertrophic cardiomyopathy

In hypertrophic cardiomyopathy, there is a sharp rapid upstroke of the carotid pulse in systole, owing to a hyperdynamic contraction due to hypertrophy, followed by rapid decline due to left ventricular outflow obstruction. The second pulse peak is thought to be related to the reflected wave.[22]

SIGN VALUE

Although documented in patients with moderate and severe aortic regurgitation,[19–21] detailed studies on its evidence base are lacking. It is rarely discovered at the bedside and, therefore, is arguably of limited value as a clinical sign.

Arterial pulse: pulsus parvus

DESCRIPTION

A small-volume pulse felt on palpation of the carotid or radial artery.

CONDITION/S ASSOCIATED WITH

- Aortic stenosis

MECHANISM/S

Aortic stenosis causes a decrease in the rate of ejection of blood from the left ventricle, while at the same time the duration of ejection is prolonged (see 'Pulsus tardus' in this section). Consequently, amplitude is decreased resulting in a smaller pulsation.

SIGN VALUE

Moderately valuable in predicting moderate to severe aortic stenosis if present,[23,24] with a sensitivity of 74–80% and specificity of 65–67% for severe aortic stenosis, and a likelihood ratio for severe aortic stenosis of 2.3.

Arterial pulse: pulsus tardus

DESCRIPTION

A pulse that has a delayed carotid peak, i.e., the peak of the pulse is felt closer to the second heart sound.

CONDITION/S ASSOCIATED WITH

- Aortic stenosis

MECHANISM/S

Thought to be caused by the combined effects of:

- flow stenosis causing a decrease in rate of ejection of blood out of the left ventricle
- compliance of the vessel distal to the stenosis
- Venturi effect.

The stenosed aortic valve reduces the speed at which blood is ejected out of the left ventricle into the aorta.

When blood flows through a stenosis, there is a pressure drop and a decrease in the rate of ejection of blood into the aorta. This is exacerbated by the Venturi effect, which sucks in the arterial wall, narrowing the arterial lumen and further delaying the arterial pulse.

In addition, recent studies[25] have shown that decreased compliance of the post-stenotic vessel damps the arterial waveform at high frequencies and, therefore, decreases downstream pulsatility, contributing to the production of a delayed pulse.

SIGN VALUE

This is a valuable arterial pulse sign. There is reasonable evidence of the value of a delayed upstroke and peak as a clinical sign.[26] Pulsus tardus is valuable in predicting the presence of severe aortic stenosis. Normally, the pulse should be felt close to S1; the closer the pulse is to S2, the more significant the stenosis. Studies[23,27–29] have shown a sensitivity of 31–90% and specificity of 68–93% with a PLR for severe aortic stenosis of 3.7.

Arterial pulse: sinus arrhythmia

DESCRIPTION

The normal physiological changes of the heart rate during inspiration and expiration can be demonstrated by feeling the peripheral pulse rate. On inspiration the heart rate quickens, on expiration it slows.

CONDITION/S ASSOCIATED WITH

None, it is physiological.

MECHANISM/S

Heart rate is predominantly mediated by the medulla and the parasympathetic nervous system via the nucleus ambiguus and, subsequently, through the vagus nerve (CNX) to the sino-atrial node. On expiration, the vagus nerve is stimulated and acts at the sino-atrial node to slow the heart down, whereas the opposite occurs on inspiration. When we breathe in, inhibitory signals are triggered and act on the nucleus ambiguus and then the vagus nerve to inhibit the parasympathetic signal to the heart. The heart rate then quickens.

SIGN VALUE

As it is a normal physiological process, if absent a pathological neuronal process may be present. However, in general it has somewhat limited value as a sign.

Bradycardia

DESCRIPTION

A heart rate of less than 60 beats per minute.

CONDITION/S ASSOCIATED WITH

The individual causes of bradycardia are too numerous to list. They include, but are not limited to:

More common

- Myocardial infarction
- Sinus node disease
- Drugs (e.g. beta blockers, calcium channel blockers, amiodarone)
- Hypothyroidism
- AV nodal disease
- Heart block
- Degeneration/ageing of the heart

Less common

- Cellular hypoxia
- Myocarditis
- Electrolyte imbalances
- Inflammatory disease (e.g. SLE)
- Obstructive sleep apnoea
- Haemochromatosis
- Congenital defect

MECHANISM/S

The individual mechanisms for each underlying cause of bradycardia are numerous. In terms of a final common pathway, bradycardia is caused by:

- an interruption to or blocking of the conduction of electrical impulses in the heart

or

- an increase in vagal tone to the heart.

The disturbance can be present at the SA node, AV node, bundle of His or left or right bundle branches.

Myocardial infarction

May cause heart block, particularly if the right coronary artery (which feeds the AV and SA nodes in the majority of people) is occluded. Failure to deliver blood to the nodes causes ischaemia and, thus, SA and AV node dysfunction.

Cellular hypoxia

Decrease in oxygen from any cause (although usually ischaemic) can cause depolarisation of the SA node membrane potential, causing bradycardia; severe hypoxia completely stops pacemaker activity.

Sinus node disease

Damage to or degeneration of the sinus node leads to a number of problems such as discharging at an irregular rate or pauses or discharges with subsequent blockage. All of these irregularities may cause bradycardia.

Heart block

Damage or disruption at the atria, AV node, bundle of His or in the bundle branches may slow conduction around the heart and cause heart block.

Electrolyte imbalances

Potassium, in particular, influences the membrane activity of cardiac myocytes as well as the SA and AV nodes. Significant variations in potassium concentration will affect membrane polarisation and heart rate. Bradycardia is more associated with hyperkalaemia than hypokalaemia, although it may be present with either.

Haemochromatosis

Iron infiltration that damages both the myocytes and conduction system of the heart has been shown to cause bradycardia.

Drugs

Drugs act by a variety of mechanisms to precipitate bradycardia:

- *Calcium channel blockers* inhibit the *slow inward* Ca^{+2} *currents* during SA node action potentials.
- *Beta blockers and muscarinics* act directly at the autonomic receptors, blocking sympathetic activity or enhancing parasympathetic activity.
- *Digoxin* enhances vagal tone to the AV node, slowing the heart rate.

SIGN VALUE

With so many potential causes of bradycardia, the specificity of the sign for a given disease is low. However, if noted in a patient who should otherwise have a normal heart rate, it is often a sign of a potentially very sick patient and warrants immediate attention.

Buerger's sign

DESCRIPTION

In patients with suspected vascular disease, when the patient lies on his/her back with the leg elevated for at least a few minutes, the foot becomes white; when the patient sits upright with the legs hanging down, the limb turns dark red.

CONDITION/S ASSOCIATED WITH

- Peripheral vascular disease

MECHANISM/S

Partial or total occlusion of the arteries of the leg by emboli or thrombosis leads to limited vascular flow to the distal leg and foot. Raising the leg further worsens arterial blood flow to the limb, causing the foot to become white. When the foot is then placed close to the ground, gravity assists flow to the distal limb and, along with compensatory peripheral vasodilatation (in response to poor perfusion), the leg quickly turns red.

SIGN VALUE

A positive Buerger's sign indicates severe limb-threatening ischaemia and should be treated immediately.

Cardiac cachexia

DESCRIPTION

A state seen in heart failure, where the patient has significant body wasting that affects all types of tissue but especially lean tissue. 'A current definition proposed is an unintentional non-oedematous weight loss of >6% of previous weight over a period of 6 months, regardless of BMI and in the absence of other cachetic states'[30] (such as cancer or hyperthyroidism).

CONDITION/S ASSOCIATED WITH

- Congestive heart failure (CHF)

MECHANISM/S

The pathway to cardiac cachexia is multi-factorial and complex. Key elements thought to be involved include:

- *Neuroendocrine abnormalities* – counter-regulatory responses to heart failure cause increased levels of angiotensin II, aldosterone, renin and catecholamine activity. These, in turn, increase basal energy expenditure and cause a catabolic shift in energy.[30]
- *Immune system activation* – myocardial injury, increased gut wall oedema and bacteria can induce an immune response that causes an over-expression of TNF-α and other cytokines. This brings about an increased metabolic rate, decreased protein synthesis, increased proteolysis and other catabolic processes.[30,31]
- *Neuroendocrine, immunological and other factors* affect the orexigenic (increased energy intake) and the anorexigenic (decreased energy intake) pathways to favour decreased energy intake and appetite.
- *Malabsorption* – gut wall oedema in CHF reduces absorption of nutrients and may alter permeability, allowing endotoxins to enter the circulation and further stimulate the immune system.[30]
- *Cellular hypoxia* – chronic low cardiac output deprives cells of normal required amounts of oxygen, producing less efficient metabolism and a shift towards catabolism rather than anabolism.[32]

SIGN VALUE

Although only seen in 13–36% of CHF patients,[30] the onset of cardiac cachexia heralds a poor prognosis.

Carotid bruit

DESCRIPTION

A high-pitched blowing systolic murmur heard on auscultation of the carotid arteries.

CONDITION/S ASSOCIATED WITH

More common

- Carotid artery stenosis

Less common

High flow states:

- Anaemia
- Thyrotoxicosis
- AV malformations

MECHANISM/S

Atherosclerosis of the common, internal or external carotid artery leads to turbulent flow, causing the bruit.

SIGN VALUE

A well studied sign of mixed value. It is present in approximately 1% of the normal adult population.[33]

In a completely asymptomatic patient, there is evidence that carotid bruits are associated with an increased risk of cerebrovascular and cardiac events.[34]

In the setting of an identified carotid stenosis, the presence of a bruit triples stroke risk.[34] However, use of bruit as a diagnostic tool has shown that it has only a variable ability to pick up high-grade stenosis with sensitivity ranging from 29% to 76% and specificity ranging from 61% to 94% (PLR from 1.6 to 5.7).[35–39]

In summary, in an asymptomatic patient who has a carotid bruit, further investigation is probably necessary. However, the characteristics of the bruit are not predictive of the level of underlying stenosis.

Cheyne–Stokes breathing

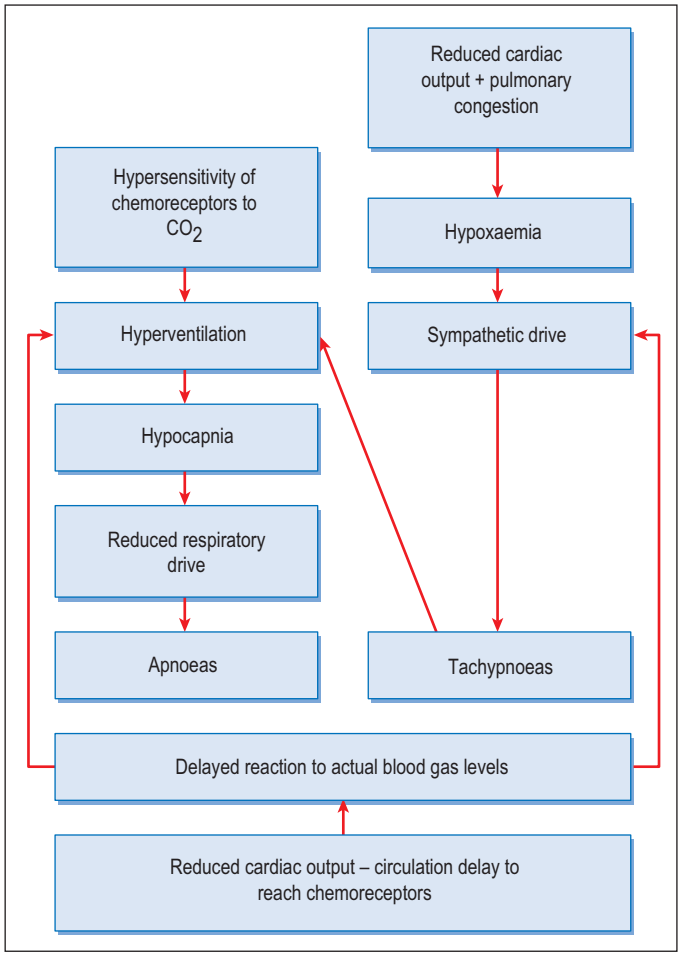

FIGURE 3.3 Flow diagram of Cheyne–Stokes respiration

DESCRIPTION

Cheyne–Stokes respiration is technically described as a breathing pattern characterised by alternating apnoeas and tachypnoeas with a crescendo–decrescendo pattern of tidal volume. In practice, what will be seen is a rhythmic waxing and waning of the depth of respiration; the patient breathes deeply for a short time and then breathes very shallowly or stops breathing altogether.[40]

CONDITION/S ASSOCIATED WITH

More common

- Congestive heart failure (CHF; 40% of patients will have Cheyne–Stokes breathing)[40]
- Stroke

Less common

- Traumatic brain injury
- Brain tumours
- Carbon monoxide poisoning
- Morphine administration

MECHANISM/S

Underlying damage or changes to the brainstem respiratory centre (which is responsible for involuntary respiration).

Mechanism/s in congestive heart failure

Several metabolic changes that affect chemoreceptors, the autonomic nervous system and the brainstem have been identified:

- Hypersensitivity of central chemoreceptors in the brainstem to changes in arterial blood carbon dioxide levels can lead to hyperventilation. This 'blowing off' causes a significant drop in carbon dioxide levels resulting in a central apnoea[41,42] (i.e. a drop in respiratory drive).
- Hypoxaemia due to lowered cardiac output and pulmonary congestion induces hyperventilation – leading to hypocapnia and an apnoea.[43]
- Hypoxaemia and hypercapnia combine to increase the sensitivity of the central breathing centre and cause an imbalance in respiration.[44]
- Heart enlargement and pulmonary congestion reduce pulmonary reservoirs of oxygen and carbon dioxide, especially during sleep, making the respiratory cycle more variable and less stable.
- With circulation delay, decreased cardiac output means it takes longer for oxygenated blood to reach peripheral chemoreceptors. This, in turn, means that changes to blood gas concentrations are often delayed and not truly representative,[43] causing an under- or over-activation of respiration.
- Increased levels of adrenaline have been seen in patients with CHF[44] due to over-activation of the sympathetic nervous system. Adrenaline increases minute ventilation, thus potentially increasing the 'blowing off' of carbon dioxide – causing hypocapnia and apnoea.

SIGN VALUE

A valuable sign, Cheyne–Stokes breathing is common in patients with an ejection fraction of less than 40%[44] and is seen in 50% of patients with CHF.[43] Studies have shown that patients with heart failure who experience Cheyne–Stokes breathing have a worse prognosis than those who do not.

Clubbing

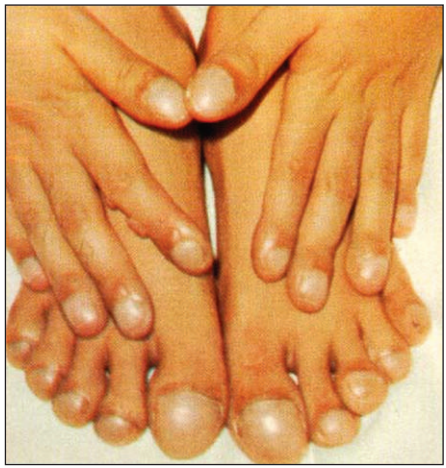

FIGURE 3.4 Clubbing of fingers and toes

Reproduced, with permission, from Marx JA, Hockberger RS, Walls RM et al (eds), *Rosen's Emergency Medicine*, 7th edn, Philadelphia: Mosby, 2009: Fig 29.2.

DESCRIPTION

A characteristic bulging of the distal finger and nail bed, often described in stages:

1. Softening of the nail bed, causing a spongy feeling when the nail is pressed
2. Loss of the normal <165° angle between nail bed and fold
3. Convex nail growth
4. Thickening of the distal part of the finger
5. Shine and striation of the nail and skin

CONDITION/S ASSOCIATED WITH

Clubbing has a large number of differential diagnoses. The vast majority of clubbing is bilateral. Unilateral clubbing is very rare and has been seen in patients with hemiplegia, dialysis fistulas and ulnar artery AV malformations.

Pulmonary and neoplastic causes are by far the most common causes (see Table 3.1).

MECHANISM/S

Many theories have been developed that attempt to explain clubbing; however, the mechanism for each aetiology is still unclear. The currently most accepted explanation involves *platelets and platelet-derived growth factor (PDGF)*.[45] Bear in mind that this theory does not explain unilateral clubbing and is obviously not applicable to all instances where clubbing occurs.

It is hypothesised that, in healthy individuals, megakaryocytes are broken down into fragments in the lungs and these fragments become platelets. If this fragmentation does not occur, whole megakaryocytes can become wedged in the small vessels of distal extremities. Once trapped, they release PDGFs, which recruit cells and promote proliferation of muscle cells and fibroblasts. This cell proliferation causes the characteristic appearance of clubbing.

Therefore, any pathology that affects normal pulmonary circulation (such as

TABLE 3.1 Causes of bilateral clubbing

Neoplastic Bronchogenic carcinoma Lymphoma Pleural tumours	**Pulmonary** Cystic fibrosis Asbestosis Pulmonary fibrosis Sarcoidosis Hypertrophic pulmonary osteoarthropathy (HPOA)
Cardiac Cyanotic heart disease Endocarditis	**Gastrointestinal** Inflammatory bowel disease Liver disease Coeliac disease
Infectious Tuberculosis Infective endocarditis HIV	**Endocrinological** Thyroid disease

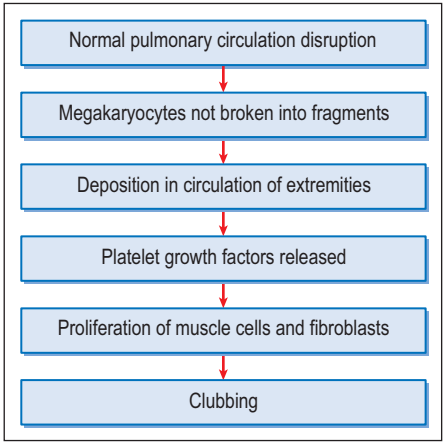

FIGURE 3.5 Proposed mechanism of clubbing

cardiac shunts or lung disease) may allow whole megakaryocytes to enter the peripheral circulation unfragmented.

In bowel disease, it is suggested that the polycythaemia and AV malformations of the lung seen in some instances contribute to this process. In addition, vascular endothelial growth factor (VEGF) has been isolated in some patients with lung cancer and HPOA and is likely to contribute to hyperplasia of the distal digits.

SIGN VALUE

Clubbing is almost always pathological and should be investigated; however, its absence does not exclude underlying disease.

Crackles (also rales)

DESCRIPTION

Popping, crackling, rattling or clicking sounds heard on lung auscultation that may be inspiratory or expiratory in timing.

CONDITION/S ASSOCIATED WITH

More common

- Left heart failure/pulmonary oedema – classically mid- to end-inspiratory
- Pneumonia
- Atelectasis
- Bronchiectasis
- Bronchitis
- Interstitial lung disease

MECHANISM/S

Heart failure

In left heart failure, raised left ventricular and atrial pressures back up into the lung vasculature. When pulmonary vasculature pressure increases above approximately 19mm Hg, a transudate of fluid enters the lung interstitium and alveoli. The alveoli are filled with fluid and collapse. When the patient breathes in, the alveoli are filled with air and 'pop' open, causing inspiratory crackles.

Pulmonary oedema

Accumulation of phlegm, debris, mucus, blood or pus in the alveoli or small airways as a result of pneumonia, haemoptysis, inflammatory disorder or any other aetiology will cause the alveoli to collapse and then potentially be 'popped' open, creating crackles.

SIGN VALUE

Crackles or rales are the most common sign in acute heart failure – seen in up to 66–87%.[46,47] In the setting of acute heart failure without concomitant lung pathology, crackles are highly specific for heart failure. They are less valuable in chronic heart failure as the compensatory increased lymphatic drainage will shift fluid away more effectively.

Cyanosis

A blue/purple discolouration of the skin and mucous membranes caused by an *absolute* increase in the quantity of deoxygenated haemoglobin in the blood.

The two final common pathways that can result in enough deoxygenated haemoglobin to cause cyanosis are:

1. an increase in venous blood in the area of cyanosis
2. a reduction in oxygen saturation (SaO_2).

The amount of deoxygenated haemoglobin needed to cause cyanosis is 50 g/L (5 g/dL). It is important to note that the total amount of haemoglobin influences the level of oxygen desaturation that needs to occur before cyanosis.

For example, in a severely anaemic patient with a haemoglobin level of 60 g/L (6 g/dL), the proportion of haemoglobin that is deoxygenated (reduced) may be 60% (36 g/L or 3.6 g/dL) and the patient would still not be cyanotic. Conversely, in a patient who is polycythaemic with a haemoglobin level of 180 g/L (18 g/dL), the deoxygenated haemoglobin may be only approximately 28% (50 g/L or 5 g/dL) and the patient may be cyanotic.

In other words, it is the *absolute* amount of deoxygenated haemoglobin that causes cyanosis, *not* the relative amount.[48]

Cyanosis: central

DESCRIPTION

A blue/purple discolouration of the tongue, lips and mucous membranes.

CONDITION/S ASSOCIATED WITH

More common

- Cardiac
  - Tetralogy of Fallot
  - Heart failure
- Respiratory
  - V/Q mismatches (e.g. due to pneumonia)
  - Hypoventilation

Less common

- Cardiac
  - Transposition of the great arteries
  - Eisenmenger's syndrome
- Haematological
  - Methaemoglobinaemia
  - Sulfhaemoglobinaemia
- Respiratory
  - Pulmonary venous fistulas
  - Intrapulmonary shunts

MECHANISM/S

In central cyanosis, the key point to remember is that *deoxygenated blood is leaving the heart*. That is, deoxygenated blood is present in the arterial circulation even before it reaches the periphery. This is due to *low oxygen saturation and/or abnormal haemoglobin.*

Cardiac

In cardiac causes of central cyanosis, the main issue is the mixing of venous and arterial blood, leading to decreased oxygen saturation. For example, in Tetralogy of Fallot, the ventricular septal defect results in mixing across the ventricles. This means the blood leaving the left side of the heart already has a lower-than-normal oxygen saturation.

Respiratory

A V/Q mismatch or shunting of blood through the lungs, without adequate oxygenation, will increase the quantity of deoxygenated haemoglobin that passes out of the lungs, leading to reduced oxygen saturation.

Cyanosis: peripheral

DESCRIPTION

Blue discolouration of the extremities, often in the fingers.

CONDITION/S ASSOCIATED WITH

Common

- Cold exposure
- Decreased cardiac output (e.g. CHF)
- Raynaud's phenomenon (see Chapter 1, 'Musculoskeletal signs')

Less common

- Arterial and venous obstruction

MECHANISM/S

Peripheral cyanosis is caused by the *slowing of blood flow and increased oxygen extraction* in the extremities.

When human bodies are exposed to cold, peripheral vasoconstriction occurs to maintain warmth. This leads to reduced blood flow to the periphery and thus effectively more time for oxygen to be taken out of the blood – hence more deoxygenated blood is present.

Similarly, in CHF, decreased cardiac output leads to vasoconstriction (to maintain blood pressure and venous return), which decreases blood flow to peripheral areas.

Ewart's sign

DESCRIPTION

A combination of the following signs:

- Dullness to percussion over the left scapula
- Aegophony (increased vocal resonance)
- Bronchial breath sounds over the left lung

CONDITION/S ASSOCIATED WITH

- Pericardial effusion

MECHANISM/S

A large pericardial effusion can compress the left lung, causing consolidation and/or atelectasis, which alters percussive resonance. If the effusion enlarges sufficiently to collapse and/or consolidate the lung, increased vocal resonance and bronchial breath sounds will be heard. (For a discussion of the mechanism of increased vocal resonance and bronchial breath sounds, see Chapter 2, 'Respiratory signs'.)

Hepatojugular reflux (also abdominojugular reflux)

DESCRIPTION

Pressing firmly over the right upper quadrant (liver area) causes the jugular venous pressure (JVP) to become more obvious and sometimes visibly higher. A positive hepatojugular reflex is present if there is an increase in JVP of more than 3 cmH_2O for longer than 15 seconds.

CONDITION/S ASSOCIATED WITH

- Any cause of right ventricular dysfunction – systolic or diastolic dysfunction
- Heart failure and volume overload
- Elevated right ventricular afterload

Note: This sign is NOT seen in cardiac tamponade.

MECHANISM/S

Putting pressure on the right upper quadrant assists in venous return to the right side of the heart via the inferior vena cava. The increased volume of blood returning to the right side of the heart is met with raised end-systolic and -diastolic pressures in the right atrium and ventricle (due to the right-sided dysfunction) and venous blood and pressure is 'backed up' into the jugular veins. *The right ventricle cannot accommodate additional venous return.*

SIGN VALUE

Useful when seen in concert with other signs or symptoms and will add to the value of a raised JVP. It is sensitive but not specific to any particular disorder and, therefore, must be taken in clinical context.

- In the presence of dyspnoea, can predict heart failure: PLR 6.0, NLR –0.7834.[49]
- In the presence of dyspnoea, can predict elevated pulmonary capillary wedge pressure >15 mmHg: PLR 6.7, NLR 0.08.[49]
- Detecting elevated left heart diastolic pressures, with sensitivity of 55–84%, specificity of 83–98%, PLR 8.0, NLR 0.3.[50]

If dyspnoea is not present, search for alternative causes of the reflux.

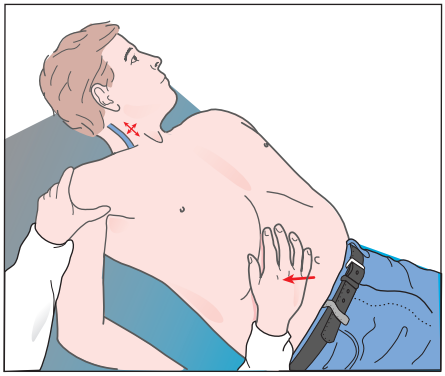

FIGURE 3.6 Hepatojugular reflux

Hepatomegaly

DESCRIPTION

Enlargement of the liver to greater than 13 cm in length (midclavicular line).

CONDITION/S ASSOCIATED WITH

- Haemochromatosis
- Hepatitis
- Congestive heart failure (CHF)
- Malignancy

MECHANISM/S

In CHF, low cardiac output or impaired right ventricular filling leads to 'backing up' of pressures into the inferior vena cava and hepatic veins. With increasing venous pressures, the liver becomes engorged and enlarged.

Hypertensive retinopathy

Refers to pathological changes seen in retinal vessels owing to (or as a marker of) hypertension. Some signs have also been used as markers for severity of underlying hypertension.

SIGN VALUE

There has recently been renewed interest in hypertensive retinopathy as a marker, prognostic indicator and risk factor for disease.[51–53]

- Mild and moderate hypertensive retinopathy is associated with a 1–2-fold increase in the risk of hypertension.
- Mild and moderate hypertensive retinopathy is associated with a 1–8-fold increase in the risk of stroke.
- Mild hypertensive retinopathy is associated with a 2–3-fold increase in the risk of coronary artery disease.
- Moderate hypertensive retinopathy is associated with increased risk of cognitive decline.

Hypertensive retinopathy: arteriovenous (AV) nipping (or AV nicking)

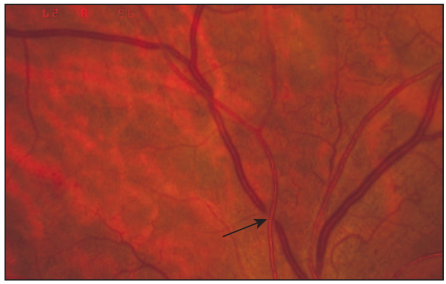

FIGURE 3.7 AV nipping/nicking

Based on Yanoff M, Duker JS (eds), *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 6-15-2.

DESCRIPTION

An enlarged retinal arteriole that crosses a vein can press down and cause swelling distal to the crossing. The vein will have an hourglass appearance on either side of the intersection.

CONDITION/S ASSOCIATED WITH

- Hypertension

MECHANISM/S

Persistently elevated blood pressure causes hyperplasia of the arteriolar media and intimal thickening.[51] The enlarged vessel impinges on the underlying vein, giving it a 'nipped in' appearance.

Hypertensive retinopathy: copper and silver wiring

DESCRIPTION

Refers to the abnormal colouring of the arterioles seen through an ophthalmoscope. In copper wiring, the arterioles appear reddish-brown; in silver wiring, the vessels look grey.

CONDITION/S ASSOCIATED WITH

- Hypertension

MECHANISM/S

The *distortion of the normal light reflex* of the retinal vessels is the cause of both discolourations.

In copper wiring, the sclerosis and hyalinisation spreads throughout the arterioles, continually thickening them. As this thickening continues, the light reflex *becomes more diffuse* and the retinal arterioles become red-brown in appearance.

In silver wiring, worsening sclerosis increases the optical density of the vessel wall, making it look 'sheathed'. If the entire vessel becomes sheathed, it will look like a silver wire.

Hypertensive retinopathy: cotton wool spots

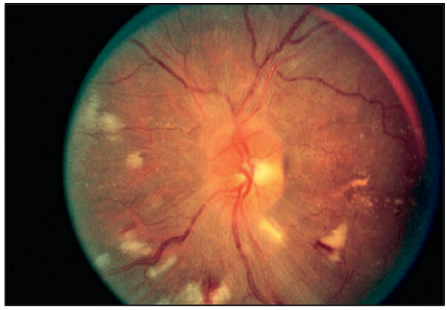

FIGURE 3.8 Cotton wool spots

White lesions with fuzzy margins, seen here approximately one-fifth to one-fourth disk diameter in size. Orientation of cotton wool spots generally follows the curvilinear arrangement of the nerve fibre layer.

Reproduced, with permission, from Effron D, Forcier BC, Wyszynski RE, Chapter 3: Funduscopic findings. In: Knoop KJ, Stack LB, Storrow AB, Thurman RJ, *The Atlas of Emergency Medicine*, 3rd edn, McGraw-Hill. Available: http://proxy14.use.hcn.com.au/content.aspx?aID=6000554 [2 Apr 2010].

DESCRIPTION

Small areas of yellow-white discolouration on the retina, often described as puffy white patches.

CONDITION/S ASSOCIATED WITH

More common

- Diabetes – most common
- Hypertension – common

Less common

- Central retinal vein occlusion
- Branch retinal vein occlusion
- HIV – rare
- Pancreatitis – rare

MECHANISM/S

Principally due to damage and swelling of the nerve fibres.

Prolonged hypertension results in distortion and blocking of retinal arterioles, blockage of axoplasmic flow (flow of proteins, lipids etc along the axon of the neuron) and a build-up of intracellular nerve debris in the nerve fibre layer. These insults result in swelling of the layer.

Hypertensive retinopathy: microaneurysms

DESCRIPTION

Small, round, dark red dots on the retinal surface that are smaller than the diameter of major optic veins (see Figure 3.9). They often herald a progression to the exudative phase of hypertensive retinopathy.

CONDITION/S ASSOCIATED WITH

- Diabetes
- Hypertension

MECHANISM/S

As progression of hypertensive retinopathy occurs, there is capillary occlusion ischaemia and degeneration of the vascular smooth muscle, endothelial cell necrosis and formation of tiny aneurysms.

Hypertensive retinopathy: retinal haemorrhage

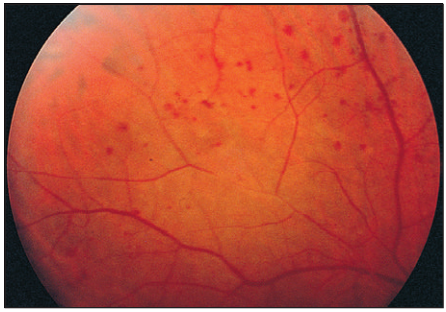

FIGURE 3.9 Dot and blot haemorrhages and microaneurysms

Reproduced, with permission, from Yanoff M, Duker JS (eds), *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 6-20-2.

DESCRIPTION

Bleeding that occurs in or spills onto the retina. Can be 'dot and blot' or 'streaking' in appearance.

CONDITION/S ASSOCIATED WITH

More common

- Hypertension
- Diabetes
- Trauma

Less common

- Retinal vein occlusions
- Retinal artery occlusions

MECHANISM/S

Prolonged hypertension leads to intimal thickening and ischaemia. This causes degeneration of retinal blood vessels to the point where they leak plasma and bleed onto the retina.[52]

Janeway lesions

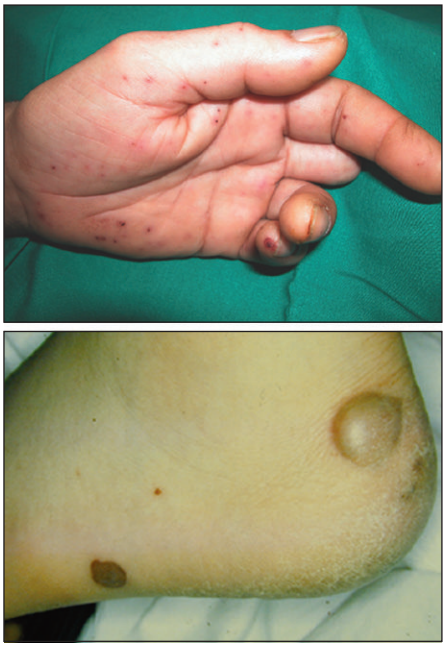

FIGURE 3.10 Janeway lesions

Based on Mandell GL, Bennett JA, Dolin R, *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th edn, Philadelphia: Churchill Livingston, 2009: Fig 195-15.

DEFINITION

Non-tender, haemorrhagic macules or papules often found on the palms or soles – especially on thenar or hypothenar eminences.[54]

CONDITION/S ASSOCIATED WITH

- Bacterial endocarditis – traditionally reported with the acute form of the disease

MECHANISM/S

The underlying mechanism is still unclear. Janeway lesions are thought to be caused by septic micro-emboli deposited in peripheral sites. However, recent histological research[54] has shown that an immunological vasculitic process may play a role in some lesions.

SIGN VALUE

Janeway lesions have limited value as a sign, appearing in only 4–10% of patients with bacterial endocarditis.[55] If present, investigations for other signs of bacterial endocarditis should be sought.

For other signs of bacterial endocarditis, see also 'Osler's nodes', 'Roth's spots' and 'Splinter haemorrhages' in this chapter.

Jugular venous pressure (JVP)

The signs associated with jugular venous pressure (JVP) are some of the first to be introduced to students studying cardiology and are some of the most useful. An understanding of the signs that can be elicited will assist patient care, as well as prepare the student or junior doctor for the inevitable questions from senior clinicians at the bedside.

JVP: Kussmaul's sign

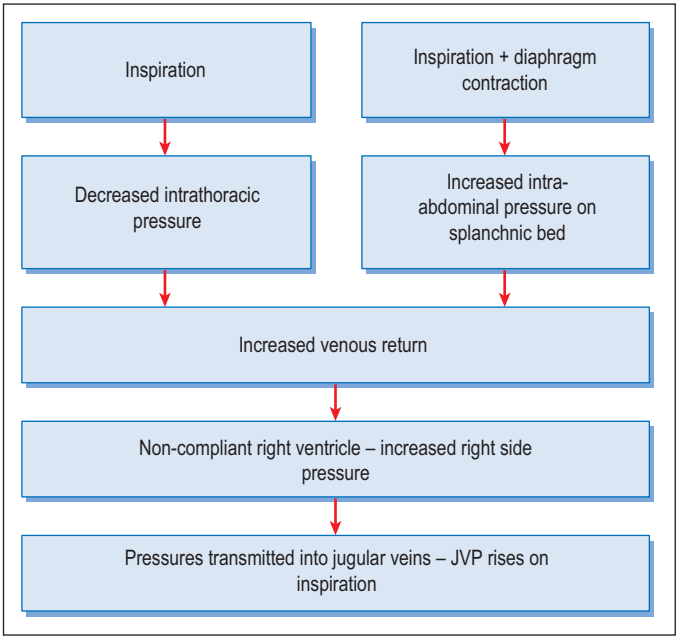

FIGURE 3.11 Mechanism of Kussmaul's sign

Based on www.clevelandclinicmeded.com/.../imagequiz25/.

DESCRIPTION

Rather than a decline in the level of the JVP on inspiration as venous blood is returned to the heart, a paradoxical rise in the JVP is seen when the patient breathes in.

CONDITION/S ASSOCIATED WITH

More common

- Severe heart failure
- Right ventricular infarction
- Pulmonary embolus

Less common

- Tricuspid stenosis
- Constrictive pericarditis

MECHANISM/S

Kussmaul's sign is thought to be caused by a combination of *increased venous return* to the heart plus a *constricted or non-compliant right ventricle*.

The process occurs as follows:

- Normal inspiration requires a decrease in intrathoracic pressure. This helps draw venous blood back toward the thorax.
- Contraction of the diaphragm on inspiration increases abdominal pressure and further increases venous return from an engorged splanchnic bed.[56]
- A non-compliant right ventricle, owing to constrictive pericarditis, failure of the right ventricle or increased right ventricular afterload (pulmonary embolus), cannot accommodate the venous return, and right atrial pressure exceeds the fall in pleural pressure.[57]
- The blood then backs up into distended neck veins.

SIGN VALUE

Kussmaul's sign may be present in less than 40% of constrictive pericarditis cases; however its specificity for an underlying pathology is very high. If present it needs to be investigated.

JVP: raised

DESCRIPTION

This refers to the level of venous pulsation in the jugular veins relative to the sternal angle. The JVP is elevated if visible higher than 3 cm from the sternal angle with the patient reclining at 45°.

The JVP is an indirect measure of right ventricular filling pressure. If filling pressure is raised, JVP is raised. It also has a predictable relationship with pulmonary wedge pressure and is useful in assessing volume status and left ventricular function.

CONDITION/S ASSOCIATED WITH

- Heart failure
- Volume overload
- Cardiac tamponade
- Pericardial effusion
- Pulmonary hypertension

MECHANISM/S

Contributing factors include:

- In patients with heart failure, the peripheral veins are abnormally constricted due to increased tissue oedema and sympathetic stimulation. This has the effect of increasing the blood volume in the central venous system – i.e. the thoracic vena caval system that enters the right side of the heart.
- *Volume overload*: like any pump system, ventricular function cannot manage excess intravascular volume indefinitely. Eventually, overload will lead to increased ventricular end-systolic and -diastolic volume and pressure, which in turn backs up through the atrium and is transmitted into the jugular veins – either directly from the right-sided dysfunction or via the lungs in left heart failure.
- *Right ventricular systolic failure*: decreased right ventricular output leads to increased end-systolic pressure, which is transmitted back to cause increased right atrial pressure. The pressure is then transmitted back into the venous system, raising venous pressure and the JVP.
- *Right ventricular diastolic failure* (e.g. constrictive pericarditis, cardiac tamponade): increased stiffness or decreased compliance of the right ventricle means end-diastolic pressure is higher for a given volume during filling. The pressure is then 'backed-up' into the venous and jugular venous system.

SIGN VALUE

Several studies have confirmed the value of a raised JVP.

If raised, the JVP can help predict raised venous pressure and volume status:

- predicting CVP >8 cmH_2O: sensitivity 47–92%, specificity 93–96%, LR if present 9.0[52,58]
- detecting CVP >12 cmH_2O: sensitivity 78–95%, specificity 89–93%, LR if present 10.4 and if absent 0.1.[52]

Another study found more value if an elevated JVP was not present:

- predicting PCWP >18 mmHg: sensitivity 57%, PPV 95%, NPV 47%.[59] However, if the raised JVP was absent, the specificity was 93% for PCWP <18 mmHg.

Raised JVP also has negative prognostic value:

- predicting heart failure admissions: RR 1.32[60]
- predicting death from heart failure: RR 1.37.[60]

A raised JVP is a key sign in pericardial disease:

- cardinal finding of cardiac tamponade in 100% of cases
- seen in 98% of patients with constrictive pericarditis.

JVP: the normal waveform

In well people, the JVP has a predictable waveform that is visible during cardiac catheterisation (as depicted in Figure 3.13). Each section represents a change in right atrial and jugular venous pressure:

- *a* – represents the contraction of the right atrium and the end of diastole
- *c* – marks the start of right ventricular contraction and blood flow, causing the tricuspid valve to bulge
- *x* – or '*x-descent*' occurs when the atrium relaxes and the tricuspid valve is pulled down to the apex of the heart
- *v* – represents atrial filling pressure after ventricular contraction
- *y* – or '*y-descent*' marks the filling of the ventricle after the tricuspid valve opens

In short, *a*, *c* and *v* all represent relative increases in atrial pressure, and *x* and *y* represent decreasing atrial pressure. Also, remember that often the *a* and *c* components are too close in timing to see except in certain clinical situations.

With this in mind, abnormalities of the different parts of the waveforms can be easily identified.

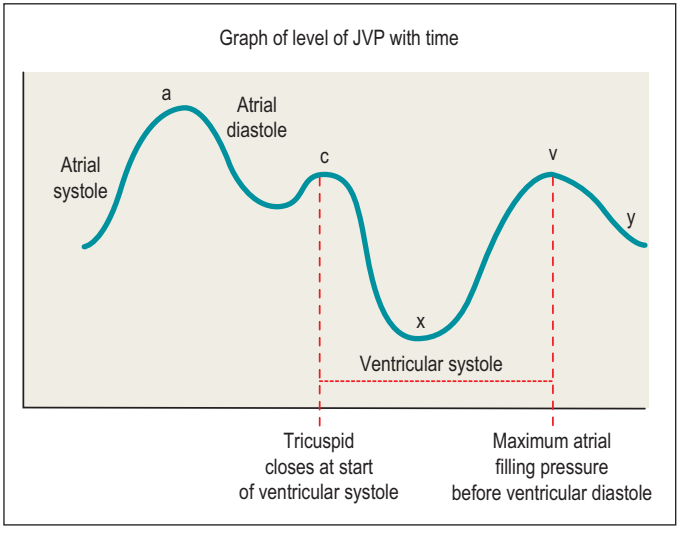

FIGURE 3.12 The normal JVP waveform

JVP waveform variations: *a*-waves – cannon

DESCRIPTION

A large, abrupt flicker/flicker of the *a*-wave that occurs after S1 and *on* the carotid pulse upstroke. Cannon *a*-waves usually do not have the prominent descent that occurs with large *v*-waves (see 'JVP waveform variations: *v*-waves – large' in this chapter).

CONDITION/S ASSOCIATED WITH

More common

- AV dissociation and complete heart block

Less common

- Atrial flutter
- Ventricular tachycardia
- Ventricular ectopics
- Atrial premature beats
- Junctional premature beats
- Severe tricuspid stenosis
- 1st degree heart block with markedly prolonged PR interval

MECHANISM/S

The underlying mechanism for almost all causes of cannon *a*-waves is a disparity in timing between atrial and ventricular contraction, resulting in atrial contraction against a closed tricuspid valve.

The *a*-wave represents the onset of atrial contraction during which there is an expected minor increase in atrial pressure, as the atrial size is momentarily reduced. Normally, the tricuspid valve opens and atrial pressure drops as blood flows into the ventricle, ventricular systole occurs and the tricuspid valve closes again.

When a disparity between atrial contraction and ventricular relaxation occurs (regardless of the cause), the atrium contracts vigorously against a closed tricuspid valve, causing a wave of increased pressure from the atrium into the jugular veins – the cannon *a*-wave.

In all of the causes of cannon *a*-waves given here, there is some degree of atrial/ventricular dyssynchrony, when the atrium is beating at various points in time against a closed tricuspid valve.

For example, in atrial flutter the atria are beating 2–4 times as fast as the ventricle, depending on the AV block. This means that at regular intervals the atrium will be contracting against a valve recently shut after the previous ventricular contraction.

In complete heart block, the atria and ventricles are operating with different pacemakers which are stimulating contractions at different times.

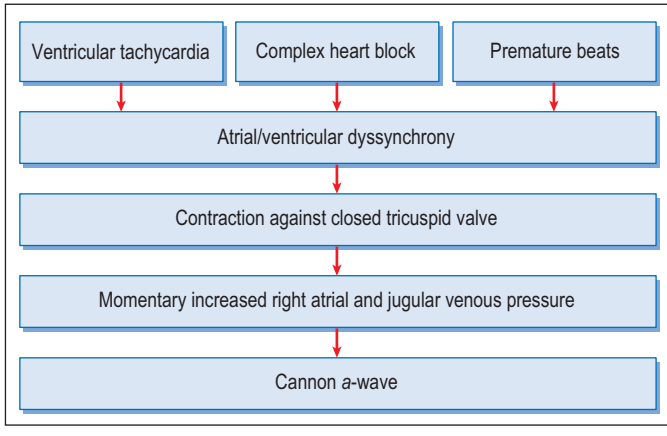

FIGURE 3.13 Mechanism underlying cannon *a*-waves

JVP waveform variations: *a*-waves – prominent or giant

DESCRIPTION

An abnormally large and abrupt outward movement of the jugular vein that occurs before the first heart sound. The 'prominent' *a*-wave *precedes* ventricular systole and the carotid pulse upstroke.

CONDITION/S ASSOCIATED WITH

- Right ventricular hypertrophy
  - Pulmonary stenosis
  - Pulmonary hypertension
- Tricuspid stenosis

MECHANISM/S

Raised right atrial pressure from resistance to ventricular filling is the common final pathway. In pulmonary stenosis and pulmonary hypertension, a higher effective afterload on the right ventricle reduces right ventricular stroke volume and raises end-systolic ventricular pressure, which backs up to cause raised right atrial pressure. This may cause (or be exacerbated by) right ventricular hypertrophy, further increasing resistance to filling and end-diastolic pressure.

In tricuspid stenosis, less blood flows into the ventricle in diastole, leaving a higher volume and pressure in the right atrium at the end of diastole. The atrium then contracts against an already raised pressure, further increasing the prominence of the *a*-wave.

POTENTIAL AREAS OF CONFUSION EXPLAINED – PROMINENT VERSUS CANNON *A*-WAVES

Prominent *a*-waves and cannon *a*-waves are hard to see and difficult to differentiate.

Two helpful tips to remember when looking at the JVP:

1. Prominent *a*-waves occur before ventricular systole, i.e. **not in time** with the carotid pulse and before S1.
2. Cannon *a*-waves occur with ventricular systole, i.e. **in time** with the carotid pulse and after S1.

JVP waveform variations: *v*-waves – large

DESCRIPTION

Usually found in patients with an elevated JVP, *v*-waves will appear as a large systolic outward distension and rise of the JVP with carotid pulsation. There is usually prominent venous collapse visible after the *v*-wave and S2 then occurs.

CONDITION/S ASSOCIATED WITH

- Tricuspid regurgitation
- Pulmonary hypertension

MECHANISM/S

Increased right atrial blood volume, due to regurgitant flow from the right ventricle during systole, leads to increased right atrial pressure that is then transmitted up into the jugular vein, leading to the characteristic *v*-wave distention.

In tricuspid regurgitation, an incompetent valve allows ventricular blood to be ejected back into the right atrium during systole. This increases right atrial pressure and JVP, causing outward distension of the veins.

In pulmonary hypertension, pressure from the pulmonary artery backs up through to the right ventricle and then the right atrium.

SIGN VALUE

The absence of large *v*-waves and raised JVP is specific for the absence of moderate or severe tricuspid regurgitation (i.e. a good NPV). However, their presence does not necessarily predict moderate or severe tricuspid regurgitation.[61]

JVP waveform variations: *x*-descent – absent

DESCRIPTION

The loss of the characteristic descent in JVP waveform that normally coincides with systole.

CONDITION/S ASSOCIATED WITH

- Tricuspid regurgitation
- Atrial fibrillation

MECHANISM/S

Normally, the *x*-descent is caused by the floor of the atrium drawing downwards during systole (see discussion under 'JVP waveform variations: *x*-descent – prominent'). In tricuspid regurgitation, the regurgitant volume offsets the normal drop in pressure caused by ventricular systole.

In atrial fibrillation, an *x*-descent is thought to be absent due to poor right ventricular contraction combined with a degree of tricuspid regurgitation.[62]

JVP waveform variations: *x*-descent – prominent

DESCRIPTION

The *x*-descent occurs in the jugular venous waveform after atrial contraction, during ventricular systole, and is timed with the carotid pulse (see Figure 3.13). It represents the decrease in JVP that occurs due to:

- atrial relaxation
- the tricuspid valve being pulled downwards during ventricular systole
- ejection of blood volume from the ventricles.

All of these aspects enlarge or relax the atrium, decreasing the atrial pressure.

A prominent *x*-descent is faster and larger than normal. It is a sign that shows that forward venous flow only occurs during systole.

It is a challenging sign to identify on clinical exam but has been proven on cardiac catheterisation.

CONDITION/S ASSOCIATED WITH

- Cardiac tamponade/pericardial effusion

MECHANISM/S

A prominent *x*-descent is an exaggeration of the normal waveform descent. In cardiac tamponade, compression of the chambers of the heart leads to elevated right atrial pressure. This raised pressure eventually blocks the forward flow of venous blood (i.e. filling) from the jugular vein into the atrium during diastole.

When the atrium relaxes and the ventricles contract in systole, the tricuspid valve is pulled down towards the apex of the heart, and there is a momentary increase in atrial volume and decrease in atrial pressure, allowing a *rapid descent* in atrial pressure and the JVP.

SIGN VALUE

Often a difficult sign to see, and there is limited evidence on the prevalence of a prominent *x*-descent; nonetheless, if suspected, cardiac tamponade must be excluded.

JVP waveform variations: *y*-descent – absent

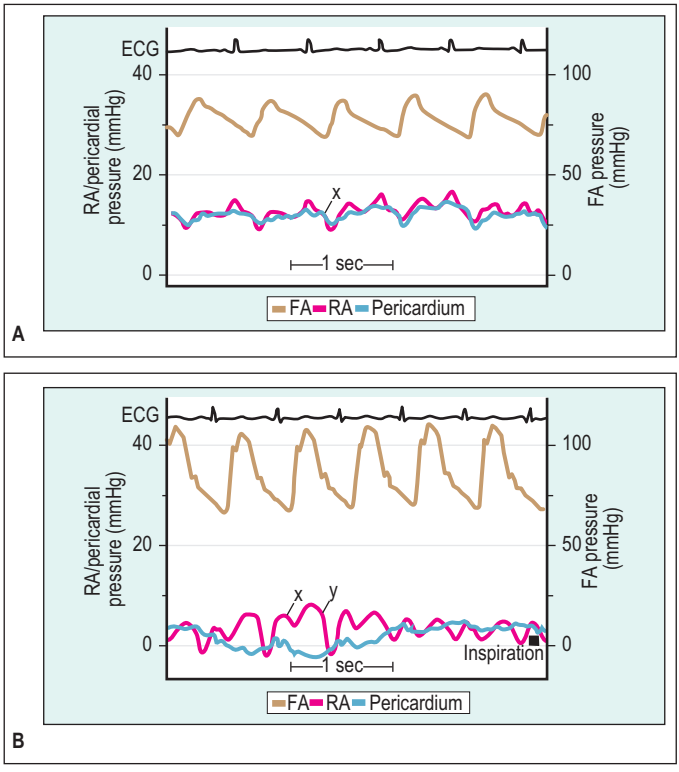

FIGURE 3.14 Absent *y*-descent in cardiac tamponade

Femoral, right atrial and pericardial pressure before (**A**) and after (**B**) pericardiocentesis in a patient with cardiac tamponade. Note that, before pericardiocentesis, there is an *x*-descent but no *y*-descent. Post pericardiocentesis there is an increase in femoral artery pressure and a decrease in right atrial pressure and the *y*-descent is now visible.

Modified from Lorell BH, Grossman W, Profiles in constrictive pericarditis, restrictive cardiomyopathy and cardiac tamponade. In: Baim DS, Grossman W (eds), *Grossman's Cardiac Catheterization, Angiography, and Intervention*, 6th edn, Philadelphia: Lippincott Williams & Wilkins, 2000: p 832.

DESCRIPTION

The *y*-descent represents the drop in right atrial pressure that occurs when the tricuspid valve opens and blood flows into the right ventricle during diastole.

CONDITION/S ASSOCIATED WITH

Most common

- Cardiac tamponade

Less common

- Tricuspid stenosis

MECHANISM/S

Any pathology that may limit or cause no ventricular filling in diastole will cause an absent *y*-descent.

In cardiac tamponade, pressure from pericardial fluid surrounding the heart leads to a higher left ventricular diastolic

pressure, which impedes filling of the ventricle during diastole and thus blunts the *y*-descent.[63]

Rarely, in tricuspid stenosis the filling of the right ventricle is impaired by the stenotic tricuspid valve. Therefore, right atrial pressure remains higher than normal and an impaired pressure descent occurs.

JVP waveform variations: *y*-descent – prominent (Friedrich's sign)

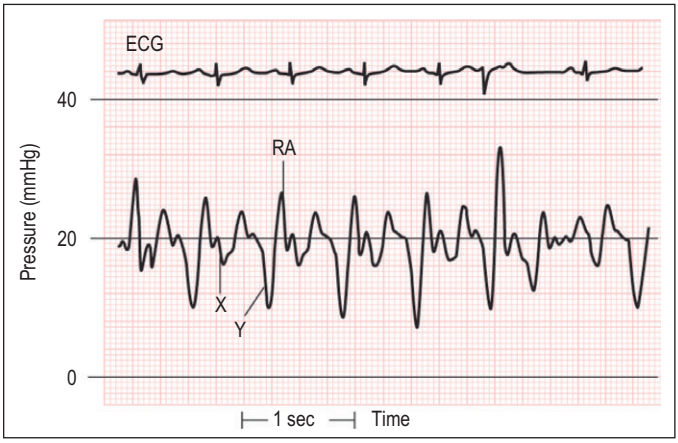

FIGURE 3.15 Prominent *y*-descent in constrictive pericarditis

Right atrial (RA) pressure recording from a patient with constrictive pericarditis. Note the elevation in pressure and prominent *y*-descent corresponding to rapid early diastolic right atrial emptying.

Reproduced, with permission, from Goldman L, Ausiello D, *Cecil Medicine*, 23rd edn, Philadelphia: Saunders, 2007: Fig 77-11.

DESCRIPTION

A faster and more prominent descent of the JVP during diastole, coinciding with the drop in right atrial pressure that occurs after opening of the tricuspid valve.

Seen clinically as an abrupt collapse of the neck veins during diastole.

CONDITION/S ASSOCIATED WITH

More common

- Constrictive pericarditis

Less common

- Right ventricular infarction
- ASD
- Atrial fibrillation

MECHANISM/S

In constrictive pericarditis, early diastolic filling is not inhibited but filling becomes impaired in the last two-thirds of diastole when the expanding ventricle hits the rigid pericardium. Once this occurs, the pressure rises again to a higher-than-normal level.

The *y*-descent appears accentuated as it descends from a higher-than-normal right atrial pressure.

SIGN VALUE

A prominent *y*-descent has been found to occur in about one-third of patients with constrictive pericarditis and two-thirds of patients with right ventricular infarction, although studies are limited and it is often difficult to see in a clinical setting.

The presence of a rapid *y*-descent excludes the diagnosis of pericardial tamponade (see 'JVP waveform variations: *y* descent – absent').

Mid-systolic click

DESCRIPTION

A non-ejection systolic click, heard shortly after S1, with radiation to the axilla. It is best heard with the diaphragm of the stethoscope over the apex with the patient in the left lateral position.

The mid-systolic click may occur in isolation or in conjunction with a late systolic mitral regurgitation murmur.

CONDITION/S ASSOCIATED WITH

- Mitral valve prolapse

MECHANISM/S

In mitral valve prolapse, the leaflets, especially the anterior leaflet, protrude into the atrium in systole. The mid-systolic click occurs when the *anterior leaflet prolapses into the atrium, putting tension on the chordae tendinae. The click corresponds to the sudden tensing of the chordae tendinae.*[64]

SIGN VALUE

When present, this sign is very specific for mitral valve prolapse; however, prolapse may be present without a mid-systolic click occurring.

Mitral facies

DESCRIPTION

A purple or plum-coloured malar flush.

CONDITION/S ASSOCIATED WITH

- Mitral stenosis

It should be noted that many causes of low cardiac output can cause mitral facies.

MECHANISM/S

Low cardiac output with severe pulmonary hypertension leads to chronic hypoxaemia and skin vasodilatation.

Murmurs

The detection and classification of murmurs is an important bedside skill. Although the six components of timing, intensity, pitch, shape, location and radiation are all required for a complete description of a murmur as a clinical sign, murmurs in this chapter will be listed, in the first instance, according to their timing and in the following order: systolic, diastolic or continuous. Table 3.2 will enable the reader to match the characteristics of the murmur they have heard with a likely cardiac pathology or vice versa. The underlying mechanism is then explained under the heading for that pathology.

TABLE 3.2 Summary of murmurs

Timing	Shape	Best heard	Common cause
SYSTOLIC			
'Ejection' systolic	Mid- to late-peaking	Aortic area radiating to carotid	Aortic stenosis
	Crescendo–decrescendo	Pulmonic area with inspiration	Pulmonary stenosis
Pansystolic/ holosystolic	Flat	Apex radiating to left axilla	Mitral regurgitation
		4th intercostal space at left sternal edge to right sternal edge increasing with inspiration	Tricuspid regurgitation (Carvello's sign)
		4th–6th intercostal spaces	VSD
Late systolic	As for mitral regurgitation but with an associated mid-systolic click	Apex radiating to left axilla	Mitral regurgitation associated with MV prolapse
DIASTOLIC			
Early	Decrescendo	Left sternal edge (aortic area)	Aortic regurgitation
	Decrescendo	Pulmonic area on full inspiration	Pulmonary regurgitation
Mid-to-late	Decrescendo	Mitral area with the bell and patient in left lateral decubitus position	Mitral stenosis
	Crescendo–decrescendo	4th intercostal space at lower left sternal edge	Tricuspid stenosis
CONTINUOUS			
	'Machinery'	Left upper chest	PDA

Murmurs – systolic: aortic stenotic murmur

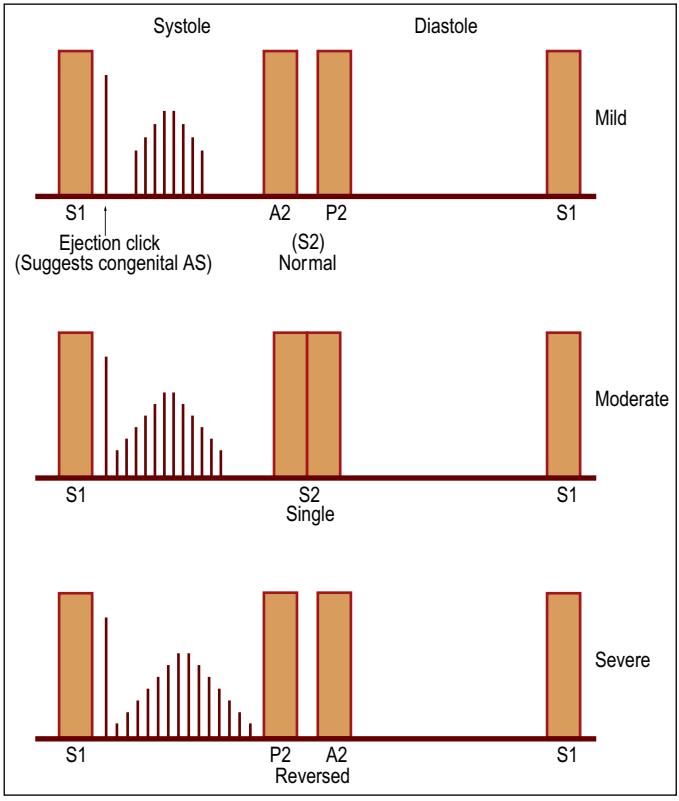

FIGURE 3.16 Timing and shape of an aortic stenotic murmur

Based on Talley N, O'Connor S, *Clinical Examination*, 6th edn, Sydney: Elsevier Australia, 2009: Fig. 4.48A.

3

DESCRIPTION

A mid-to-late-peaking ejection systolic murmur best heard over the aortic area of the praecordium that radiates to the carotid arteries. It is late-peaking and ceases before A2. Manoeuvres that increase stroke volume (such as squatting) will increase the volume of the murmur, while manoeuvres increasing afterload (e.g. standing and Valsalva) will reduce volume.

CONDITION/S ASSOCIATED WITH

- Age-related degeneration/calcification – most common cause
- Rheumatic heart disease – common cause
- Congenital bicuspid valve and calcification
- Congenital aortic stenosis

MECHANISM/S

Most causes of aortic stenosis eventually result in progressive damage to and calcification of the valvular apparatus, leading to narrowing or obstruction of the area of the valve and/or stiffening of the leaflets. Blood flowing over the stenotic valve in systole causes the murmur. The mechanisms leading to this common pathway vary depending on the underlying pathology.

Age-related degeneration ('senile calcification')

This was initially thought to be due to normal, continuous mechanical stress over many years. The current proposed mechanism involves inflammatory changes, lipid accumulation, up-regulation of

immunological mediators and ACE activity leading to *calcification and bone formation*.[26]

Rheumatic heart disease

In all instances of rheumatic heart disease, a type 2 hypersensitivity reaction to group A streptococcus (GAS) causes damage to the heart valve.

Antibodies directed against the M protein of the GAS cross-react and act against normal myocardium, joints and other tissues by virtue of molecular mimicry. The M protein antigen of the GAS 'looks like' normal self antigens, which are therefore attacked by the body's immune system.

The resulting reaction leads to the characteristic changes of rheumatic heart disease:

- fusion of the commissures and cusps
- adhesion formation and stiffening of the leaflets
- thickening of leaflet edges
- shortened, thickened chordae tendinae.

Consequently, valve area is diminished and the valve cannot open as wide or as efficiently.

SIGN VALUE

This sign is best used in conjunction with other clinical findings. If present, it is of reasonable value in determining the presence of aortic stenosis (sensitivity of 96%, specificity of 71%, PLR 3.3[65,66]). The likelihood of the aortic stenosis is further increased in the presence of a delayed carotid upstroke, absent S2 and a humming quality to the murmur.[67]

The radiation of the murmur is very helpful in identifying aortic stenosis. Should a systolic murmur radiate from the aortic area across the praecordium to the apex in a 'broad apical-to-base pattern', the LR is 9.7.[67]

The absence of certain findings also aids in the *exclusion* of aortic stenosis as the cause of the murmur. Studies have shown that the absence of characteristic aortic stenotic murmur is very helpful in excluding aortic stenosis with an LR of 0.10,[65,66] as is the absence of radiation of the murmur to the carotids, LR 0.2 (0.1–0.3).[67]

The intensity of the murmur does not indicate severity. Body size and cardiac output are more important determinants.[66] In fact, a softer aortic stenotic murmur may indicate severe disease!

Murmurs – systolic: mitral regurgitation murmur

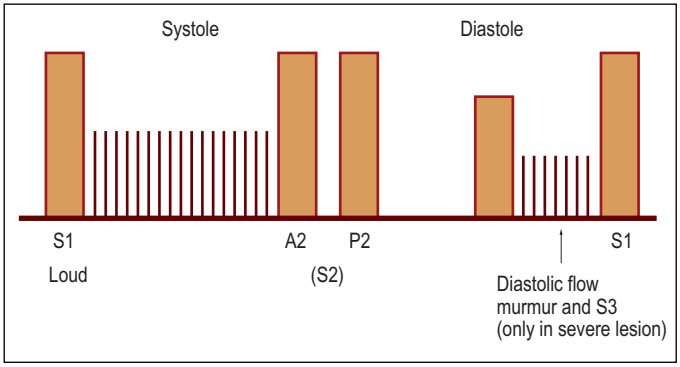

FIGURE 3.17 Timing and shape of mitral regurgitation murmur

Reproduced, with permission, from Talley N, O'Connor S, *Clinical Examination*, 6th edn, Sydney: Elsevier Australia, 2009: Fig. 4.46A.

3

See also 'Mid-systolic click' in this chapter.

DESCRIPTION

A high-pitched, pan-systolic, blowing murmur heard loudest at the apex and radiating to the left axilla. It varies little with beat-to-beat changes in stroke volume.

CONDITION/S ASSOCIATED WITH

Any damage or disruption to the mitral apparatus (mitral leaflets, chordae tendinae, papillary muscles, mitral annulus) can cause mitral regurgitation and, therefore, there are numerous potential causes.

More common causes

- Mitral valve prolapse
- Rheumatic heart disease
- Infective endocarditis
- Myxomatous degeneration
- Cardiomyopathy
- Ischaemic heart disease

GENERAL MECHANISM/S

To cause a mitral regurgitation murmur, the underlying disease or pathology must disrupt the mitral apparatus so that the valve does not close effectively. Thus, during systole a jet of blood moves back across into the left atrium. This turbulent regurgitant jet moving across an incompletely closed valve causes the murmur.

Rheumatic heart disease

Thickening of the valve leaflets and stiffening of the commissures prevents normal closure of the mitral valve.

Infective endocarditis

In infective endocarditis, infection of the valve and the resulting inflammatory process can destroy any part of the valvular apparatus, rendering the valve unable to close or remain closed effectively during systole.

Cardiomyopathy

In dilated cardiomyopathy of any cause, the left ventricle enlarges, as does the mitral annulus. Consequently, the mitral leaflets are unable to effectively cover the valvular orifice, allowing a regurgitant jet of blood back into the left atrium.

Ischaemic heart disease

In ischaemic heart disease, a myocardial infarction may cause mitral regurgitation through a variety of mechanisms:

- papillary muscle rupture or elongation causing leaflet prolapse
- dysfunction of the papillary muscles preventing tightening of the chordae tendinae and effective closure of the mitral valve
- regional remodelling and changes in ventricular size and function that cause annular dilatation and affect papillary muscle function and mitral leaflet coaptation.

Myxomatous degeneration

A genetic defect in the composition of the collagen in the valvular apparatus allows *stretching and elongation of the leaflets and chordae tendinae*. This increases the risk of

the chordae rupturing and leaflets prolapsing into the left atrium on systole.

SIGN VALUE

The characteristic mitral regurgitation murmur has moderate value in detecting the presence of mitral regurgitation with a sensitivity of 56–75%, specificity of 89–93% and an LR of 5.4.[68,69] It does not, however, indicate the severity of the regurgitation.

Specifically, the radiation of the systolic murmur is also helpful in predicting mitral regurgitation. A 'broad apical pattern', with the murmur extending from the fourth or fifth intercostal space to the midclavicular or anterior axillary line, has a PLR of 6.8 for significant mitral regurgitation.[67]

The absence of mitral regurgitation murmur is very good at predicting no significant mitral regurgitation, with an LR of only 0.2 if absent.[68,69]

Murmurs – systolic: pulmonary stenotic murmur

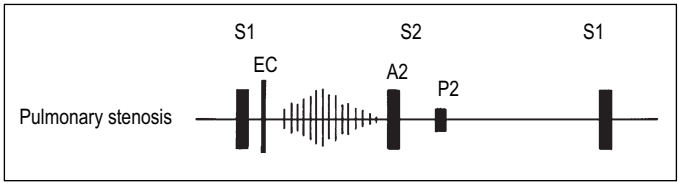

FIGURE 3.18 Timing and shape of a pulmonary stenotic murmur

Reproduced, with permission, from Keane JF et al (eds), *Nadas' Pediatric Cardiology*, 2nd edn, Philadelphia: Saunders, 2006: Fig 31-6.

DESCRIPTION

Classically, the pulmonary stenotic murmur is described as a systolic crescendo–decrescendo ejection murmur. It is heard best in the pulmonary area of the praecordium and increases with inspiration.

CONDITION/S ASSOCIATED WITH

- Congenital heart disease – most common cause
- Carcinoid syndrome – uncommon
- Rheumatic heart disease – rare

MECHANISM/S

As in other forms of stenotic lesions, turbulent blood flow across either abnormally functioning leaflets or a constricted valve orifice causes the pulmonary stenotic murmur.

Congenital

Abnormalities in development of the valvular, subvalvular or peripheral pulmonary arteries can cause a pulmonary stenotic murmur. Abnormalities include, but are not limited to, dysplastic irregularly thickened valve leaflets, a smaller-than-normal annulus and bicuspid valves.

Carcinoid syndrome

Carcinoid syndrome produces pulmonary stenosis via the deposition of plaques on or around the pulmonary valve, obstructing the orifice and/or affect the valve opening. The cause of the plaques is thought to be associated with high serotonin levels that stimulate fibroblast proliferation[70] and activation; however, the exact mechanism is still unclear.

Murmurs – systolic: tricuspid regurgitation murmur (also Carvello's sign)

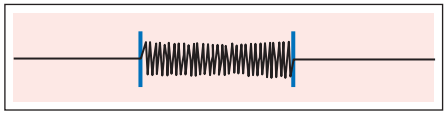

FIGURE 3.19 Tricuspid regurgitation is a pan-systolic murmur, heard over the left sternal edge, that is louder on inspiration

Reproduced, with permission, from Libby P et al, *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 8th edn, Philadelphia: Saunders, 2007: Fig 11.9B.

More common

- Any cause of right ventricular dilatation – most common cause
- Rheumatic heart disease
- Infective endocarditis

Less common

- Ebstein's anomaly and other congenital abnormalities
- Prolapse
- Carcinoid syndrome
- Papillary muscle dysfunction
- Connective tissue disease
- Trauma

DESCRIPTION

A high-pitched, pan-systolic murmur that gets louder on inspiration, heard best over the left sternal edge in the fourth intercostal space.

CONDITION/S ASSOCIATED WITH

A variety of diseases may cause tricuspid regurgitation. Most commonly, it is secondary to dilatation of the right ventricle and not to disease of the valve itself. Causes of tricuspid regurgitation include:

GENERAL MECHANISM/S

An incompetent tricuspid valve allows blood to flow back from the right ventricle to the right atrium during systole. *The flow across the incompetent valve causes the murmur.*

As in other valvular disorders, a malfunction or anomaly in the valve itself, the annulus[71] or any other part of the valvular apparatus that does not allow *normal coaptation of valve leaflets* can cause tricuspid regurgitation.

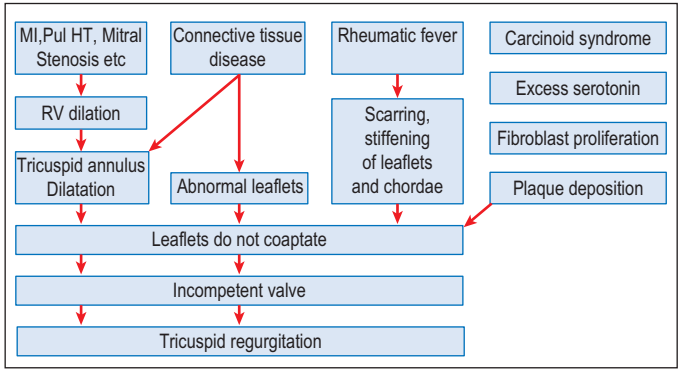

FIGURE 3.20 Mechanisms of tricuspid regurgitation

Based on Pennathur A, Anyanwu AC (eds), Seminars in Thoracic and Cardiovascular Surgery 2010; 22(1): 79–83.

Right ventricular dilatation

This is the *most common* cause of tricuspid regurgitation. In itself, the valve is normal. Right ventricular failure and dilatation of any cause (e.g. myocardial infarction, pulmonary hypertension, mitral valve disease leading to secondary right ventricular dilatation including the tricuspid annulus) does not allow proper coaptation of the leaflets, leading to regurgitation during systole.

Carcinoid syndrome

Excessive serotonin stimulates fibroblast proliferation and plaque development, and deposition on the endocardium and valvular apparatus causes the tricuspid valve to adhere to the ventricular wall.[72]

Connective tissue disease

Abnormalities in the connective tissue and collage produce a 'floppy' abnormal valve and may also produce dilatation of the annulus, both of which contribute to poor coaptation of leaflets and, therefore, tricuspid regurgitation.

Rheumatic fever

As in mitral and aortic rheumatic heart disease (see 'Aortic stenosis murmur', 'Mitral regurgitation murmur'), scarring and stiffening of the valve and the chordae tendinae reduces mobility and the ability of the valve to close properly.

SIGN VALUE

If present, it has a strong PLR (14.6)[68] for mild-to-severe tricuspid regurgitation being present. Additional signs may aid the identification of triscuspid regurgitation. Early systolic outward movement of the neck veins (*v*- or *cv*-waves, LR of 10.9) and hepatic pulsation (LR 12.1) significantly increase the likelihood that tricuspid regurgitation is present.[67]

If not present, this does not rule out mild-to-severe tricuspid regurgitation – NLR of 0.8.[68]

Murmurs – systolic: ventricular septal defect murmur

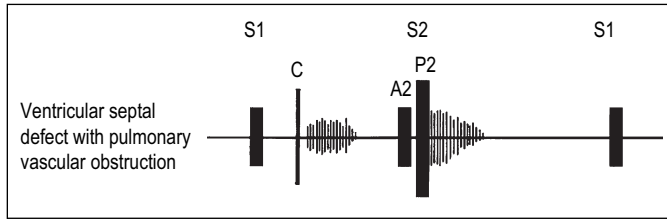

FIGURE 3.21 Timing and shape of ventricular septal defect murmur
Based on Avery ME, First LP [eds]. *Pediatric Medicine. Baltimore: Williams & Wilkins*, 1989.

DESCRIPTION

A pan-systolic, high-pitched murmur heard best in the fourth to sixth intercostal spaces that does *not* radiate to the axilla and does not increase with inspiration.

Condition/s associated with

- Ventricular septal defect

MECHANISM/S

A pressure gradient across the defect and turbulent flow are the principal factors involved in the mechanism.

The left ventricle experiences much higher pressure than the right ventricle. The septal defect allows blood to go from a region of high pressure to the low pressure of the right ventricle. Turbulent flow across the orifice creates the murmur.

SIGN VALUE

The intensity of the murmur may be a guide to the size of the defect – the smaller the defect, often the louder the murmur.[73]

Murmurs – diastolic: aortic regurgitation murmur

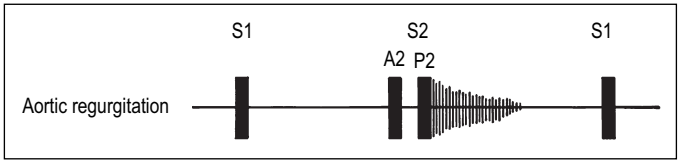

FIGURE 3.22 Timing and shape of an aortic regurgitation (AR) murmur

Reproduced, with permission, from Keane JF et al (eds), *Nadas' Pediatric Cardiology*, 2nd edn, Philadelphia: Saunders, 2006: Fig 33-20.

DESCRIPTION

A high-pitched, decrescendo, blowing diastolic murmur that is best heard over the aortic area of the praecordium.

CONDITION/S ASSOCIATED WITH

Any process that can lead to damage to or destruction of the aortic valve, including but not limited to:

More common

- Rheumatic valve disease
- Bacterial endocarditis
- Connective tissue disorders (e.g. Marfan's syndrome)

Less common

- Age-related degenerative change
- Aortic dissection
- Syphilis
- Takayasu disease
- Ankylosing spondylitis
- Other inflammatory diseases (e.g. SLE, Reiter's syndrome)

MECHANISM/S

The final common pathway for aortic regurgitation (AR) is damage to and/or incompetence of the valvular apparatus – this causes blood to flow back into the left ventricle in diastole. The characteristic murmur is the sound of blood moving back across the damaged aortic valve.

The different diseases causing AR can affect either the valve cusps and leaflets or the aortic root and are mediated by a number of immunological, degenerative and/or inflammatory mechanisms or else via a traumatic process.

SIGN VALUE

Hearing an AR murmur warrants further investigation. It is a valuable sign whose absence is a good indication that moderate to severe AR is absent (LR 0.1).[74] Its sensitivity and specificity in predicting moderate to severe regurgitation are 88–98% and 52–88%, respectively.[68,75–77]

Similarly, the presence of an AR murmur significantly increases the chance of the presence of mild or more serious AR (LR 8.8–32.0).[74]

Murmurs – diastolic: eponymous signs of aortic regurgitation

AR has classically been associated with a large number of eponymous signs (see Table 3.3). Although these are interesting to elicit and impressive to recite, the mechanisms underlying them and their true value are often unclear.

TABLE 3.3 Eponymous signs of aortic regurgitation (AR)

Sign	Description	Mechanism	Sign value
Austin Flint murmur	A low-pitched rumbling murmur, starting in mid-diastole and finishing at end of diastole. It is best heard over the cardiac apex with the patient leaning forward and breathing out. Mitral stenosis must be absent.	Postulated mechanisms include: • Regurgitant aortic blood flow traps leaflets of the mitral valve, leading to a form of mitral stenosis • Fluttering of mitral valves due to the AR jet flow • Endocardial vibrations caused by AR jets	Opinions vary as to the value of the sign. Austin Flint murmur is most likely to be heard in the setting of severe aortic regurgitation and has wide variations in sensitivity from 25% to 100%, depending on the study.[78] Another review has suggested that the presence of Austin Flint's murmur indicates moderate to severe AR with LR of 25![79]
Becker's sign	Pulsation of the retinal arteries		Limited evidence
Corrigan's sign (water hammer or collapsing pulse)	Rapid visible arterial pulsations with a noticeable increase in amplitude of peripheral pulses	Increased arterial wall compliance	Corrigan's sign is of limited usefulness with sensitivity of 38–95% and specificity of 16% for presence of AR[78]
De Musset's sign	Rhythmic head bobbing in synchrony with the heart beat	Unclear	Limited evidence
Duroziez's sign	To-and-fro murmur or 'machinery' murmur heard over the femoral artery in diastole and systole, when compressed with a stethoscope	Systolic murmur caused by forward flow into distal artery; diastolic murmur caused by AR back towards heart	Sensitivity of 35–100%, specificity of 33–81% for presence of significant AR; studies lack consistent quality and power[78]
Gerhardt's sign	Pulsatile spleen		Limited evidence

Continued

TABLE 3.3 Eponymous signs of aortic regurgitation (AR)—cont'd

Sign	Description	Mechanism	Sign value
Hill's sign	Higher systolic blood pressure in the legs than the arms If the foot/arm blood pressure difference is greater than 60 mmHg or if there is an increase in the popliteal/brachial gradient of more than 20 mmHg, this is a positive Hill's sign	No clear understanding of the underlying mechanism	Conflicting evidence from limited studies: • A recent study showed no true increase in intra-arterial lower extremity blood pressures compared to upper limb blood pressures in patients with AR[80] • Another study showed the popliteal/brachial gradient predicted severity of AR with an increase in gradient >20 mmHg with a sensitivity of 89%, but the sign does not distinguish between mild or no AR[79] • In predicting presence of AR, specificity of 71–100% and sensitivity ranging from 0% to 100%[79]
Mayne's sign	A fall in diastolic blood pressure of >15 mmHg with arm elevation		Limited evidence
Müller's sign	Pulsatile uvula		Limited evidence
Quincke's sign	Exaggerated pulsations of the capillary nail bed. May be accentuated by depressing and releasing the distal end of the nail		Limited evidence
Traube's sign	A sharp or 'pistol shot'-like sound heard over the femoral artery	Sudden expansion and tensing of vessel walls in systole[30]	Limited evidence

Murmurs – diastolic: Graham Steell murmur

DESCRIPTION

A high-pitched, early diastolic, blowing decrescendo murmur best heard in the pulmonary area of the praecordium on full inspiration. It is a pulmonary regurgitative murmur in the setting of pulmonary hypertension.

CONDITION/S ASSOCIATED WITH

- Pulmonary regurgitation (PR) with pulmonary hypertension – often secondary to lung disease. (Note: PR does *not* cause pulmonary hypertension!)

MECHANISM/S

Pulmonary hypertension (usually above 55–60 mmHg) leads to increased pressure on the pulmonary valve and annulus. *Dilatation of the annulus occurs* and the valve becomes incompetent. The high-flow jet of blood across the incompetent valve creates the murmur.

Murmurs – diastolic: mitral stenotic murmur

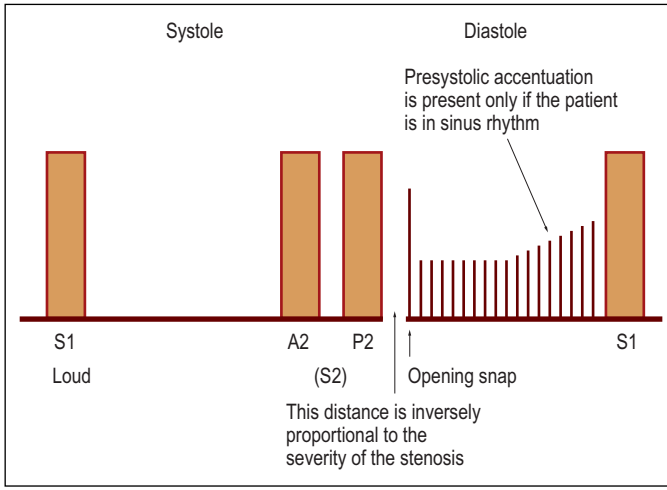

FIGURE 3.23 Timing and shape of a mitral stenotic murmur

Based on Talley N, O'Connor S, *Clinical Examination*, 6th edn, Sydney: Elsevier Australia, 2009: Fig. 4.45 A.

DESCRIPTION

A diastolic low-pitched, rumbling murmur best heard with the bell of the stethoscope over the mitral area of the praecordium with the patient in the left lateral decubitus position.

CONDITION/S ASSOCIATED WITH

- Rheumatic heart disease – almost exclusively
- Congenital mitral stenosis – rare

MECHANISM/S

Diastolic blood flow across a damaged, narrow valve.

The immunological mechanism in rheumatic heart disease is discussed under 'Aortic stenotic murmur' under 'Murmurs – systolic' in this chapter. It is thought that repeated acute subclinical rheumatic attacks, continued chronic rheumatic activity or haemodynamic trauma leads to progressive fibrosis, calcification and thickening of the valvular apparatus[26] and causes poor leaflet opening during diastole and narrowing of the valvular orifice.

With the valve narrowed, the blood flow across it in diastole is turbulent and produces the characteristic murmur.

SIGN VALUE

Very specific for mitral stenosis and should be investigated if heard.

Murmurs – diastolic: opening snap (OS)

DESCRIPTION

Brief, sharp, high-pitched sound heard in early diastole.

CONDITION/S ASSOCIATED WITH

- Mitral stenosis

MECHANISM/S

Not completely clear.

It is most likely caused by the sudden stop in movement of the mitral dome into the left ventricle, combined with a sudden increase in the velocity of blood moving from the atrium into the ventricle.[81]

Put more simply, the stenotic calcified valve tends to form a 'dome' shape during diastole, as the left ventricle attempts to suck blood into its cavity. Although initially mobile, the calcification of the valve will abruptly stop further movement, causing an opening snap.[82]

SIGN VALUE

There is limited evidence on the value of this sign. However, there are some characteristics that assist in ascertaining the degree of mitral stenosis:

- The A2-to-opening snap interval is inversely proportional to the degree of left atrial to left ventricle diastolic pressure gradient. In other words, the shorter the interval between A2 and the opening snap, the larger the gradient and the worse the stenosis.[26]
- The louder the S1 or opening snap, the less the mitral valve is actually calcified.[81]
- Very severe mitral stenosis may not be associated with an opening snap – the valve may be too stiff to open fast enough for a snap to occur.

Murmurs – diastolic: pulmonary regurgitation murmur

DESCRIPTION

In the absence of significant pulmonary hypertension, described as an early decrescendo murmur heard best over the third and fourth intercostal spaces on the left sternal edge. As with other right-sided murmurs, it will become louder on inspiration.

CONDITION/S ASSOCIATED WITH

More common

- Pulmonary hypertension – most common cause, especially in association with Eisenmenger's syndrome
- Post surgical repair of Tetralogy of Fallot in which the pulmonary valve has been cut across
- Dilated pulmonary artery – idiopathic or secondary to a connective tissue disorder (e.g. Marfan's syndrome)
- Infective endocarditis

Less common

- Congenital malformations of the structure of the valvular apparatus
- Rheumatic heart disease – rare
- Carcinoid syndrome – rare

MECHANISM/S

A pulmonary regurgitation (PR) murmur is caused by an incompetent pulmonary valve allowing blood to flow back across from the pulmonary artery to the right ventricle in diastole. Regardless of the underlying cause, this can be due to:

- dilatation of the valve ring
- dilatation of the pulmonary artery
- abnormal valve leaflet morphology
- congenital abnormalities pertaining to the valve.

Dilatation of the valve ring as a result of prolonged pulmonary hypertension is the most common cause and mechanism (see 'Graham Steell murmur' in this section).

Dilatation of the pulmonary artery, thereby effectively 'outgrowing' the pulmonary valve, may occur idiopathically or in connective tissue disorders.[26]

SIGN VALUE

Mild degrees of pulmonary stenosis are common within the community. However, the presence of a significant PR murmur increases the likelihood of PR, LR 17.0.[68]

The absence of a murmur does not rule out the presence of PR, NLR 0.9.[68]

Murmurs – diastolic: tricuspid stenotic murmur

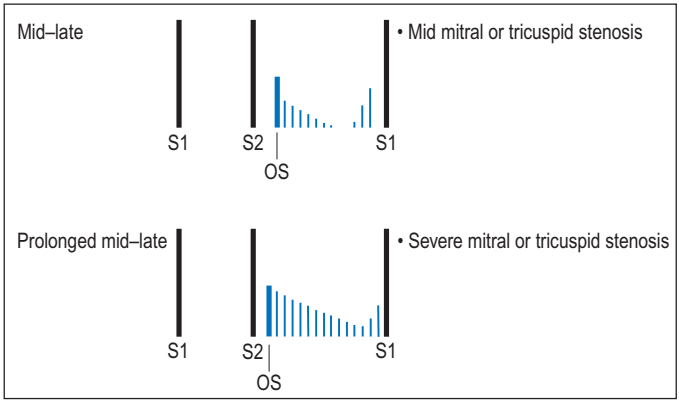

FIGURE 3.24 Timing and shape of tricuspid stenotic murmur

Reproduced, with permission, from Blaustein AS, Ramanathan A, Cardiology Clinics 1998; 16(3): 551–572.

3

DESCRIPTION

A soft, diastolic, crescendo–decrescendo murmur heard loudest over the tricuspid area of the praecordium (lower left sternal edge in the fourth intercostal space).

It is often seen and confused with mitral stenosis, and it is also seen with tricuspid regurgitation.

CONDITION/S ASSOCIATED WITH

More common

- Rheumatic heart disease – most common[83]

Less common

- Congenital tricuspid atresia and other congenital abnormalities
- Carcinoid syndrome
- Tumours – rare

MECHANISM/S

Turbulent diastolic flow across a narrowed, damaged or abnormal tricuspid valve causes the murmur.

As with other valves affected by rheumatic heart disease, thickened valve leaflets, stiffened commissures and shortened and stiff chordae tendinae restrict valve opening and cause blood flow across the valve to be turbulent.

Only 5% of tricuspid stenosis is clinically significant;[83] however, a tricuspid stenotic murmur is always abnormal and warrants investigation.

Murmurs – continuous: patent ductus arteriosus murmur

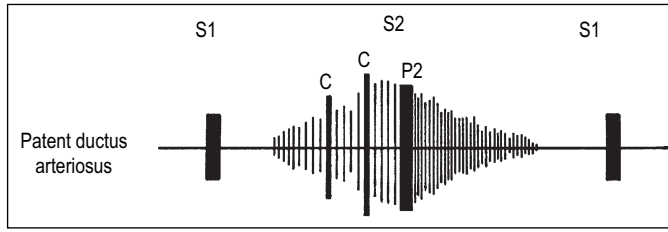

FIGURE 3.25 Timing and shape of a patent ductus arteriosus murmur

Reproduced, with permission, from Keane JF et al (eds), *Nadas' Pediatric Cardiology*, 2nd edn, Philadelphia: Saunders, 2006: Fig 35-3.

DESCRIPTION

A persistent, 'machinery' murmur that exists throughout systole and diastole, which is best heard over the left upper chest.

CONDITION/S ASSOCIATED WITH

- Patent ductus arteriosus

MECHANISM/S

For a continuous murmur to exist, there must be a persistent gradient over structures in diastole and systole.

In patent ductus arteriosus, where there is persistent connection between the aorta and pulmonary artery, blood flows from the high-pressure system of the aorta into the lower-pressure pulmonary artery, producing the 'first half' of the murmur. In diastole there is still a higher pressure in the aorta than in the pulmonary artery so blood continues to go across the patent ductus – producing the 'second half' of the murmur.

Osler's nodes

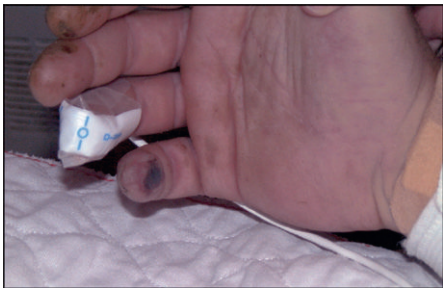

FIGURE 3.26 Osler's nodes in infective endocarditis

Reproduced, with permission, from Goldman L, Ausiello D, *Cecil Medicine*, 23rd edn, Philadelphia: Saunders, 2007: Fig 76-2.

DEFINITION

Tender, red-purple, slightly raised, cutaneous nodules often with a pale surface. Most frequently found over the tips of the fingers and toes, but can be present on the thenar eminences[54] and are often painful.

CONDITION/S ASSOCIATED WITH

More common

- Bacterial endocarditis

Less common

- SLE
- Disseminated gonococcus
- Distal to infected arterial catheter

MECHANISM/S

As in the case of Janeway lesions, the mechanism behind this sign is still unclear. Osler's nodes are thought to differ from Janeway lesions by having an underlying immunological or vasculitic process; however, some histological studies have shown evidence to also support an embolic process.

SIGN VALUE

Estimated to be seen in only 10–25% of bacterial endocarditis.[84] The low sensitivity makes the absence of Osler's nodes of limited value.

For other signs of bacterial endocarditis, see 'Janeway lesions', 'Roth's spots' and 'Splinter haemorrhages' in this chapter.

Pericardial knock

DESCRIPTION

An early-diastolic, high-pitched sound heard best between the apex of the heart and the left sternal border.

CONDITION/S ASSOCIATED WITH

- Constrictive pericarditis

MECHANISM/S

The sudden slowing of blood flow into the ventricle in early diastole that occurs when the ventricle meets the rigid pericardial sac.[85,86]

SIGN VALUE

Classically taught as one of the cardinal signs of constrictive pericarditis, it may be seen in 24% to 94% of patients with this condition.[85,86]

POTENTIAL AREAS OF CONFUSION EXPLAINED – THE THIRD HEART SOUND VERSUS PERICARDIAL KNOCK

The mechanism is similar to that of the third heart sound, and differentiating the two can be difficult. However, a pericardial knock is a high-pitched sound whereas the third heart sound is classically a low-pitched sound. As always, history and other clinical signs should be used to assist in differentiation.

Pericardial rub

DESCRIPTION

A grating or scratching sound heard throughout the cardiac cycle. It is classically described as having three components, one during diastole and two during systole.

CONDITION/S ASSOCIATED WITH

- Pericarditis

MECHANISM/S

Inflammation causes the pericardial and visceral surfaces of the pericardium (which are normally separated by a small amount of fluid) to rub together.

Peripheral oedema

DEFINITION

An abnormal accumulation of fluid under the skin or within body cavities, causing swelling of the area or indentations on firm palpation.

CONDITION/S ASSOCIATED WITH

Diseases associated with peripheral oedema are numerous. Main causes include:

More common

- Congestive cardiac failure
- Liver disease
- Nephrotic syndrome
- Renal failure
- Venous insufficiency
- Drug side effects
- Pregnancy

Less common

- Hypoalbuminaemia
- Malignancy

MECHANISM/S

The main mechanism underlying peripheral oedema is dependent on the underlying pathology. However, regardless of aetiology, either one or a combination of the following factors is present:

1. increased venous or hydrostatic pressure – raising capillary hydrostatic pressure (increased pressure pushing fluid out)
2. reduced interstitial hydrostatic pressure (reduced pressure pushing fluid into vessels)
3. decreased plasma oncotic pressure (decreased proteins keeping fluid in the vessel)
4. increased interstitial oncotic pressure (increased proteins trying to draw fluid out of vessels)
5. increased capillary leakiness
6. blocked lymphatic system – decreased ability to draw fluid and proteins away from interstitium and return them to the normal circulation.

Mechanism in heart failure

Increased venous hydrostatic pressure causes a transudative process in which fluid is 'pushed out' of vessels into the interstitium. It is normally seen in the context of *right* heart failure.

Factors contributing to this include:

- *Increased plasma volume* – decreased cardiac output (either via right or left heart failure) leads to renal hypoperfusion. In response to this, the RAAS is activated and salt and water are retained, leading to increased venous and capillary hydrostatic pressure.
- *Raised venous pressure* – ventricular dysfunction leads to increased end-systolic and/or -diastolic pressures – these pressures are transmitted back to the atrium and then to the venous system, increasing venous and capillary hydrostatic pressure.
- Increased hydrostatic pressure forces fluid out of venous vessels into surrounding tissues.
- The lymphatic system is unable to keep up with the task of reabsorbing additional interstitial fluid and oedema develops.

Liver disease

Contrary to popular belief, the main factor in the development of oedema in liver failure is *vasodilatation of the splanchnic bed*. It is not necessarily a consequence of the liver failing to produce its normal proteins (leading to hypoalbuminaemia), although this may contribute.

In liver failure increased nitric oxide and prostaglandins are present in the splanchnic circulation. This vasodilates the splanchnic vessels, leading to more blood being 'pooled' there, with less effective circulating volume driven through the kidneys, leading to an aberrant neurohormonal response that results in increased salt and water retention through the RAAS, increasing hydrostatic pressure.[87]

Nephrotic syndrome

The mechanism of oedema in nephrotic syndrome has not been completely worked out. Factors involved include:

- Massive protein loss through the kidneys and hypoalbuminaemia, decreased plasma oncotic pressure – i.e., there are fewer proteins keeping fluid in, so fluid leaks out.
- Loss of circulating volume triggers a neurohormonal response with increased salt and water retention, increasing

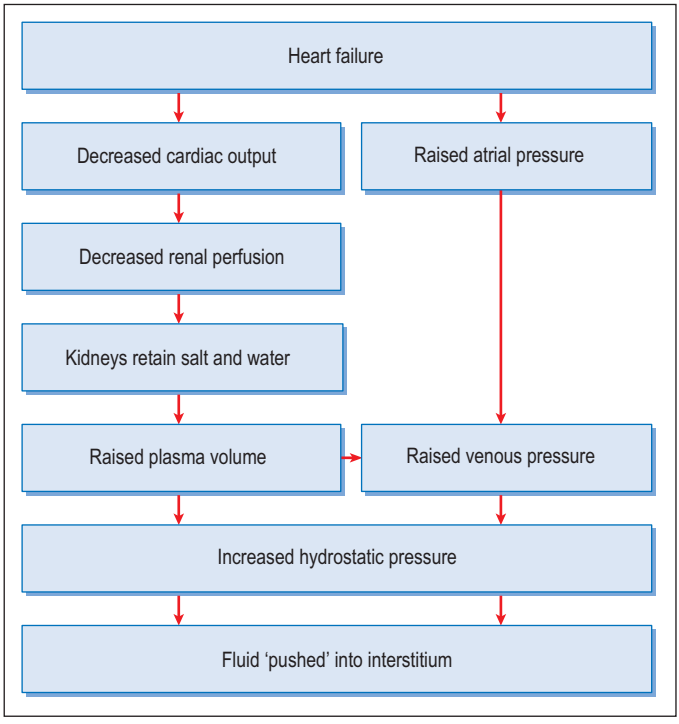

FIGURE 3.27 Peripheral oedema in heart failure

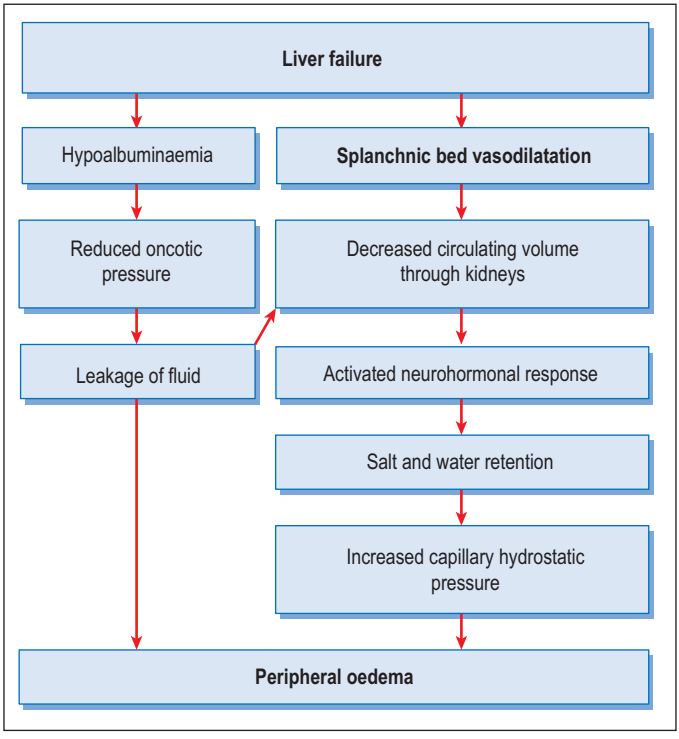

FIGURE 3.28 Peripheral oedema in liver failure

capillary hydrostatic pressure – pushing fluid out.
- Blunted hepatic protein synthesis contributes to the low quantity of proteins in the serum.
- Blunted atrial natriuretic response (ANR) – the normal response to volume overload is to excrete more salt and thus water out via the kidneys.
- The renal impairment seen in nephrotic and nephritic syndromes does not allow the 'normal' amount of salt to be excreted, thus fluid is retained. This is possibly the predominant mechanism in the absence of massive protein loss.[87]

SIGN VALUE

Peripheral oedema is a useful sign when present; however, its absence does not exclude heart failure (sensitivity 10%, specificity 93%[88]) with only 25% of patients with chronic heart failure under 70 years of age having oedema.

In liver failure the development of peripheral oedema, and in particular ascites, heralds a poor prognosis.

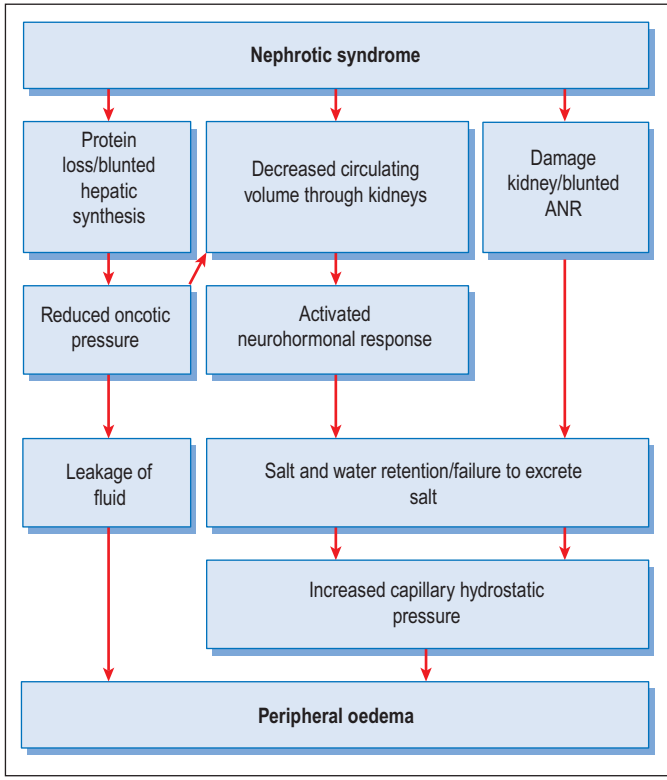

FIGURE 3.29 Peripheral oedema in nephrotic syndrome

Pulse pressure

Pulse pressure is calculated as systolic blood pressure minus diastolic blood pressure. The normal range is 40 mmHg. A variation in pulse pressure has significant clinical implications. The determinants of pulse pressure are not straightforward. The key elements are thought to be arterial resistance, arterial compliance and stroke volume/cardiac output.[89]

Pulse pressure: narrow

DESCRIPTION

A pulse pressure that is less than 20 mmHg.

CONDITION/S ASSOCIATED WITH

Common

- Heart failure
- Aortic stenosis
- Hypovolaemia – shock

Less common

- Hypertrophic cardiomyopathy
- Mitral stenosis

MECHANISM/S

Remember that systolic blood pressure represents the *maximum* pressure in systole, whereas diastolic pressure represents the *minimum* pressure in the arteries when the heart is in diastole. *Decreased cardiac output and increased systemic resistance* form the common pathway to a narrowed pulse pressure.

In practice, this means that any condition that results in a reduced cardiac output (systolic blood pressure) with maintained resistance of the arterial tree (diastolic pressure) can cause a narrow pulse pressure.

Cardiac failure

In heart failure, a low stroke volume (due to heart dysfunction) leads to more sympathetic outflow and higher (or maintained) systemic vascular resistance in order to preserve blood pressure and assist venous return to the heart. Therefore, systolic blood pressure is lowered (due to decreased cardiac output) and diastolic blood pressure is maintained (increased systemic vascular resistance), creating a narrow pulse pressure.

Shock

In the early stages of hypovolaemic shock, catecholamine levels are high as the body tries to raise peripheral vascular resistance and thus maintain venous return to the heart. This boost in peripheral vascular resistance increases diastolic blood pressure and, as a consequence, narrows the pulse pressure.

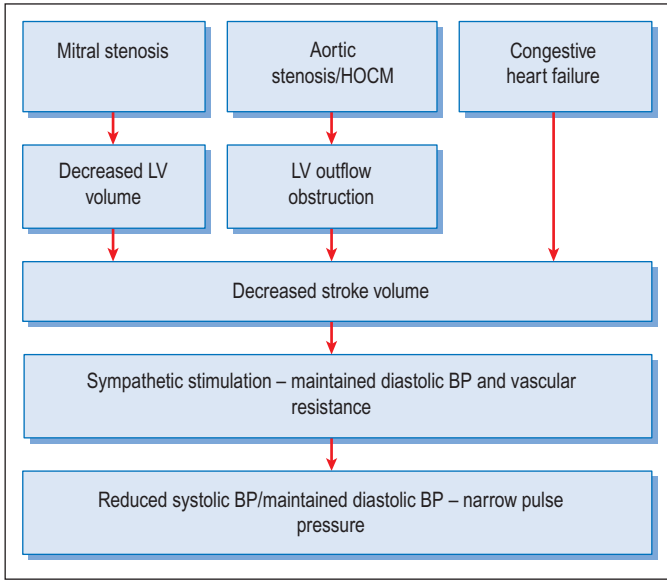

FIGURE 3.30 Narrow pulse pressure mechanism

Pulse pressure: widened

DESCRIPTION

A pulse pressure that is greater than 55–60 mmHg.

CONDITION/S ASSOCIATED WITH

Most common

- Old age
- Aortic regurgitation
- Septic shock – end-stage
- High cardiac output states
- Hyperthyroidism

MECHANISM/S

Old age

The factors determining pulse pressure in healthy patients are complex and cannot be explained by one model. However, *decreased arterial compliance and increasing pulse wave velocity* are thought to be central to the widened pulse pressure seen in older patients.

As humans age there is fragmentation and disruption of the lamina of the artery and alteration in the collagen-to-elastin ratio. These changes make the arteries stiffer and less compliant. When this occurs the artery loses its ability to accommodate the pressure rise that normally occurs in systole and, thus, the pressure increases even further (see Figure 3.34).

A second model has shown that greater arterial stiffness results in faster transmission of the arterial waveform, as there is less compliance or 'give' in the arteries to damp the waveform. A consequence of this is the faster return of the wave and augmentation of the systolic pressure, further raising systolic pressure and, therefore, pulse pressure.[48]

In summary, just knowing that increased arterial stiffness/decreased compliance and increased pulse wave velocity are present would be more than enough to explain increased pulse pressure in older patients.

Septic shock

In 'warm' septic shock, the principal cause of a widened pulse pressure is vasodilatation, increased endothelial permeability and reduced peripheral vascular resistance.

In septic shock, infection causes an immunological inflammatory reaction. Humoral and innate immune responses are activated, leading to recruitment of white blood cells and release of a number of cytokines, including TNF-α, IL-8, IL-6, histamine, prostaglandins and nitric oxide. These cytokines increase *vascular permeability and systemic vasodilatation*, reducing systemic vascular resistance and diastolic blood pressure and, hence, widening the pulse pressure.

It should be noted that septic shock can present (especially early on) as 'cold' shock with the peripheral vasculature shut down and peripheral vascular resistance maintained.

Aortic regurgitation

The high pulse pressure can be attributed to the high-volume flow from the left ventricle into the ascending aorta during systole. The diastolic decay of the pulse is attributed to the backflow into the ventricle and to forward flow through peripheral arterioles.[8]

Hyperthyroidism

Thyroid hormone has many effects on the cardiovascular system, among others. The consequences include increased blood volume, increased cardiac inotropy and decreased vascular resistance, which all contribute to widened pulse pressure.

Excess thyroid hormone increases thermogenesis in the peripheral tissues, causing vasodilatation and decreased systemic vascular resistance and diastolic blood pressure. In addition, T3 also has the direct effect of decreasing vascular resistance.

At the same time, thyroid hormone is a positive inotrope and chronotrope and also increases haematopoesis and blood volume, therefore increasing cardiac output and systolic blood pressure.

SIGN VALUE

A widened or increased pulse pressure is a very valuable sign, depending on the clinical situation in which it is encountered.

Pulse pressure is an independent predictor of mortality and morbidity in

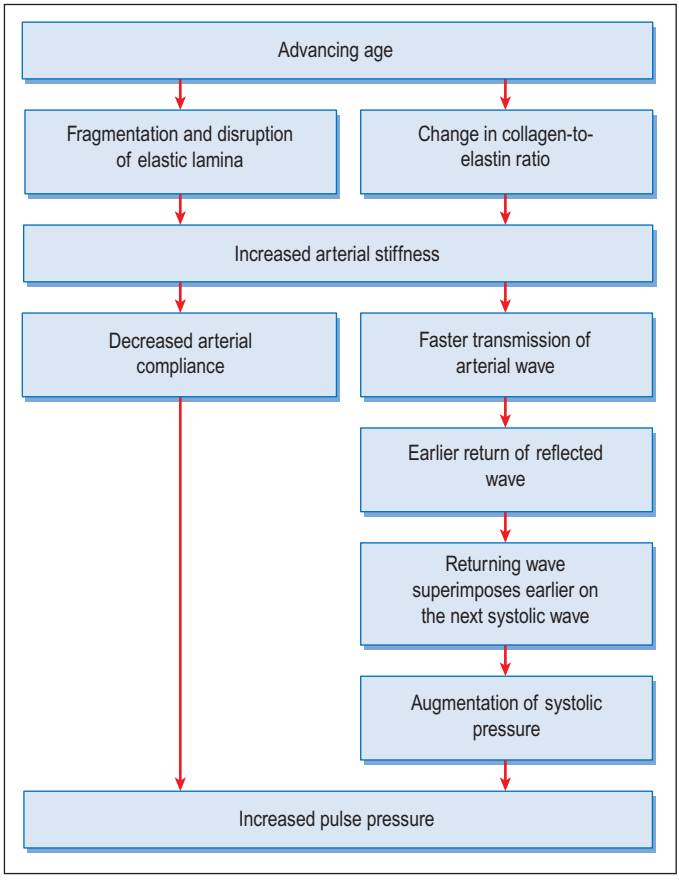

FIGURE 3.31 Mechanism of widened pulse pressure in old age

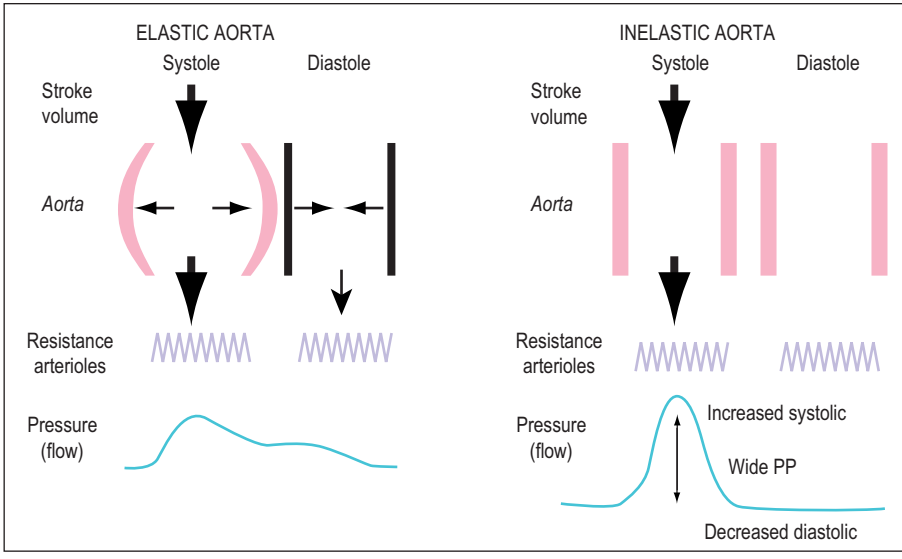

FIGURE 3.32 Widened pulse pressure and stiff vessels

Based on Lip GYH, Hall JE, *Comprehensive Hypertension*, 1st edn, Philadelphia: Mosby, 2007: Fig 11-3.

normotensive and hypertensive patients.[90,91] Furthermore, some studies suggest that pulse pressure is a better indicator of risk than diastolic and systolic blood pressure,[92–94] although not all studies agree with this.

There is strong evidence that a higher pulse pressure increases the risk of atrial fibrillation[95] and the risk of heart failure and that treating chronic widened pulse pressure or isolated systolic hypertension reduces the risk of adverse outcomes.[96]

Pulsus paradoxus

DESCRIPTION

Dr Adolph Kussmaul first named this sign in 1873 when he noticed that there was a discrepancy between the absence of a peripheral pulse and a corresponding heart beat on inspiration in patients with constrictive pericarditis. The paradox refers to the fact that heart sounds can be heard on auscultation but a radial pulse cannot be felt.

The definition of pulsus paradoxus is usually an inspiratory fall in systolic blood pressure exceeding 10 mmHg.[97] It is elicited by inflating the blood pressure cuff to above systolic pressure and noting the peak systolic pressure during expiration. The cuff is then deflated until the examiner can hear the Korotkoff sounds during inspiration and expiration, and this pressure value is noted. When a difference between these two pressures of greater than 10 mmHg occurs, pulsus paradoxus is present.[98]

CONDITION/S ASSOCIATED WITH

More common

- Cardiac tamponade
- Asthma

Less common

- Large pulmonary embolus
- Tension pneumothorax
- Large pleural effusions
- Acute myocardial infarction
- Volvulus of the stomach
- SVC obstruction
- Diaphragmatic hernia
- Constrictive pericarditis (it is commonly argued that it does not occur in constrictive pericarditis – see the box 'Potential areas of confusion explained – Pulsus paradoxus versus Kussmaul's sign in constrictive pericarditis and cardiac tamponade' below)

GENERAL MECHANISM/S

In a healthy person the radial pulse decreases in amplitude on deep inspiration. This is because breathing in causes a decrease in intrathoracic pressure, drawing more venous blood into the right ventricle. The right ventricle enlarges and the interventricular septum impinges on the left ventricle, impeding blood flow into the left ventricle. In addition, during inspiration the lungs expand, allowing more blood to pool in the pulmonary vasculature. This increase in blood pooling in the lungs combines with the impingement on the left ventricle to decrease stroke volume from the left ventricle and, hence, reduces peripheral pulses.

The mechanism behind pulsus paradoxus is an exaggeration of this normal respiratory physiology and, in general, can be caused by the following mechanisms:[98,99]

- a limitation in increase in inspiratory blood flow to the right ventricle and pulmonary artery
- greater than normal pooling of blood in the pulmonary circulation
- wide variations in intrathoracic blood pressure during inspiration and expiration – with the pulmonary pressure being more negative compared to the left atrium; as a result, blood is pulled back from the left atrium to the pulmonary veins during inspiration, thus decreasing the amount of blood available for stroke volume[99]
- impedance of venous return to the left ventricle.

Cardiac tamponade

Fluid within the pericardial sac impairs left ventricular filling but does not tend to impair right ventricular filling to the same extent.[98] When impaired filling is combined with the pooling of blood in the lungs on inspiration, it exaggerates the normal decrease of left atrial and ventricular filling on inspiration. In addition to this, pulmonary venous pressure tends to be lower than the pressure in the left atrium, resulting in a decrease in left ventricular filling as more blood is pulled back towards the pulmonary veins.[98]

Massive pulmonary embolism

A massive pulmonary embolism causes right ventricular dysfunction or failure. Less blood is able to be pumped out of the right ventricle due to the high pulmonary artery pressure. This decreased RV output, coupled with pooling of blood in the lungs, reduces left atrial and ventricular filling and, hence, stroke volume.[98]

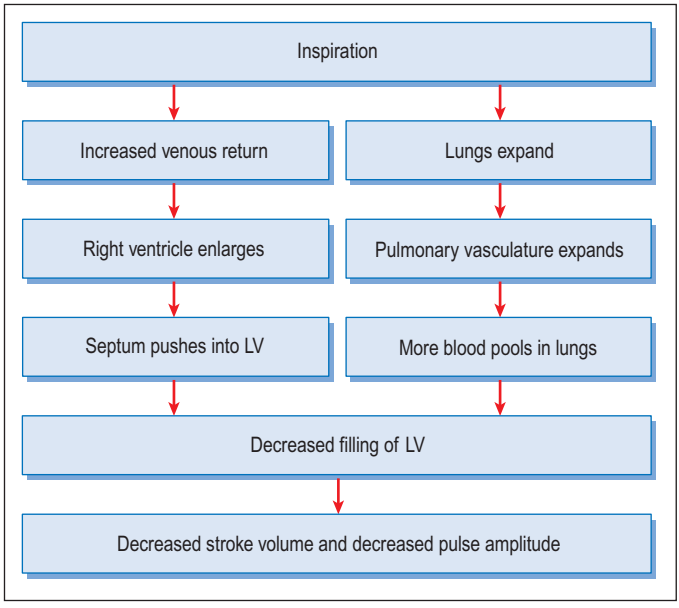

FIGURE 3.33 Normal variations in pulse with the respiratory cycle

Respiratory disorders

The main mechanism in respiratory disorders is thought to be unusually wide intrathoracic variations that are transmitted to the aorta and right side of the heart.[98,99]

In episodes of airways resistance, or loaded breathing, the negative intrathoracic pressure seen on inspiration is greater than normal, and on expiration the intrathoracic pressure is higher. The net result of this is an exaggeration of the normal physiological response outlined previously.[100]

During inspiration with airways resistance, the increased negative intrathoracic pressure draws more blood into the right ventricle and right pulmonary arteries, leaving less blood in the left side of the heart, resulting in a smaller stroke volume.[100]

During expiration the opposite occurs with more blood moving to the left side of the heart giving a greater stroke volume. Thus, airways resistance exaggerates the normal process, resulting in pulsus paradoxus.

SIGN VALUE

If accurately demonstrated, pulsus paradoxus is an extremely useful sign. In one study[101] it had a sensitivity of 98% and specificity of 83% and a PLR of 5.9 and an NLR of 0.03. Although an alternative pooled analysis[102] found a sensitivity of 82%, given its reasonably high sensitivity and low NLR, in the setting of a pericardial effusion the absence of pulsus paradoxus suggests cardiac tamponade is not present.

In the setting of asthma, it is a foreboding sign indicating imminent respiratory failure.

POTENTIAL AREAS OF CONFUSION EXPLAINED – PULSUS PARADOXUS VERSUS KUSSMAUL'S SIGN IN CONSTRICTIVE PERICARDITIS AND CARDIAC TAMPONADE

There is often confusion regarding the pathological settings in which pulsus paradoxus and Kussmaul's sign occur and why one occurs and the other does not.

Traditional teaching tells us that pulsus paradoxus occurs in cardiac tamponade and Kussmaul's sign in constrictive pericarditis, and the two are mutually exclusive. The reasoning behind this is as follows.

In constrictive pericarditis, the normal negative intrathoracic pressure present on inspiration is not passed through the rigid pericardial shell to the atria and ventricles of the heart. As a result, on inspiration, the normal right-sided augmented *filling does not occur*, and the *septum does not impinge* on the left ventricle (as occurs in pulsus paradoxus) and *does not affect left ventricular stroke volume* in the same way as it does in cardiac tamponade.

In severe pericardial constriction, inspiration does not draw venous blood back to the heart, but it coincides with elevated right atrial and ventricular pressures and distends jugular veins instead, as the heart cannot accumulate returning blood – Kussmaul's sign.

Constrictive pericarditis = Kussmaul's sign

Cardiac tamponade = pulsus paradoxus

Although this is the simple rule to follow, it should also be mentioned that pulsus paradoxus can be seen in up to one-third of cases of constrictive pericarditis.[42]

Radial–radial delay

DESCRIPTION

A disparity between the timing of pulses felt when simultaneously palpating the left and right radial pulse.

CONDITION/S ASSOCIATED WITH

- Coarctation of the aorta
- Subclavian stenosis due to aneurysm

MECHANISM/S

A coarctation or narrowing of the aorta occurs before the origin of the left subclavian artery, limiting the blood flow and causing a pressure drop distal to the narrowing. The pulse wave will arrive later in the left arm and the amplitudes of the left and right pulses will be different.

Radio-femoral delay

DESCRIPTION

Reduced amplitude and delayed timing of the pulses in the arteries of the lower body with respect to the pulses of the arteries in the upper body are classic features of aortic coarctation.[8]

CONDITION/S ASSOCIATED WITH

- Coarctation of the aorta

MECHANISM/S

As in aortic stenosis, coarctation will cause a decrease in the rate of ejection of blood due to vessel narrowing and the Venturi effect, sucking the walls inwards and contributing to a reduction in the flow and amplitude of the pulse distal to the occlusion.

In addition, the following factors are essential in the mechanism of a pulse seen in any type of coarctation:[8]

- The coarctation creates a pulse wave reflection site that is much closer to the heart. This means the pulse wave is reflected earlier and faster, creating a higher blood pressure proximal to the stricture.
- There are fewer cushioning properties (i.e. less compliance of the arterial segment involved proximal to the coarctation), further increasing blood pressure at or just prior to the stricture.
- The flow and pressure pulsations are damped in the long and dilated collateral vessels that form to provide flow distal to the coarctation.[8]

Right ventricular heave

DESCRIPTION

On palpation along the left parasternal border, a sustained impulse that peaks in early- to mid-systole is felt to 'lift' the examiner's hand.

CONDITION/S ASSOCIATED WITH

Situations in which increased right ventricular pressure load and right ventricular hypertrophy are present.[1]

More common

- Pulmonary embolism
- Pulmonary hypertension

Less common

- Tetralogy of Fallot
- Severe mitral regurgitation
- Severe mitral stenosis

GENERAL MECHANISM/S

Increased pressure load causes right ventricular hypertrophy and displacement of the right ventricle closer to the chest wall.

Mitral regurgitation

In mitral regurgitation, the left atrium provides a cushion under the heart while increased volume in systole displaces the ventricle anteriorly,[1] causing the cardiac impulse to be felt for longer and the sensation of a right ventricular heave. This, however, is very uncommon.

Roth's spots

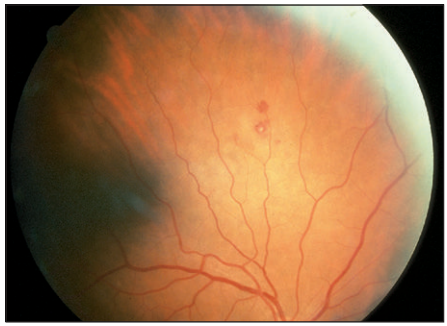

FIGURE 3.34 Roth's spots

Reproduced, with permission, from Talley N, O'Connor S, *Clinical Examination*, 6th edn, Sydney: Elsevier Australia, 2009: Fig 4-42.

DESCRIPTION

Round, white-centred retinal haemorrhages.

CONDITION/S ASSOCIATED WITH

While initially thought to be pathognomonic for subacute bacterial endocarditis, Roth's spots are seen in many conditions including:

More common

- Infective endocarditis
- Anoxia

Less common

- Myelodysplastic syndromes
- Intracranial haemorrhage
- Diabetes
- Shaken baby syndrome

MECHANISM/S

Roth's spots are *not* caused by bacterial emboli. The currently accepted theory is based on capillary rupture and fibrin deposition.

By this mechanism, insult causes rupturing of the retinal capillaries, followed by extrusion of whole blood, leading to platelet activation, the coagulation cascade and a platelet fibrin thrombus. The fibrin appears as the white lesion within the haemorrhage.[103]

The initial insult varies depending on underlying pathology:

- It is suggested that, in subacute bacterial endocarditis, thrombocytopenia secondary to a low-grade disseminated intravascular coagulopathy can prompt capillary bleeding in the retinal vasculature.
- Anaemia may cause further anoxic insult to retinal capillaries in patients with subacute bacterial endocarditis and leukaemia.
- Raised venous pressure may lead to capillary endothelial ischaemia and, hence, rupture of the capillary.

SIGN VALUE

Given the many possible causes of Roth's spots and the fact that they are only seen in less than 5%[84] of patients with bacterial endocarditis, their value as a sign independent of other clinical signs is limited.

For other signs of bacterial endocarditis, see 'Janeway lesions', 'Osler's nodes' and 'Splinter haemorrhages' in this chapter.

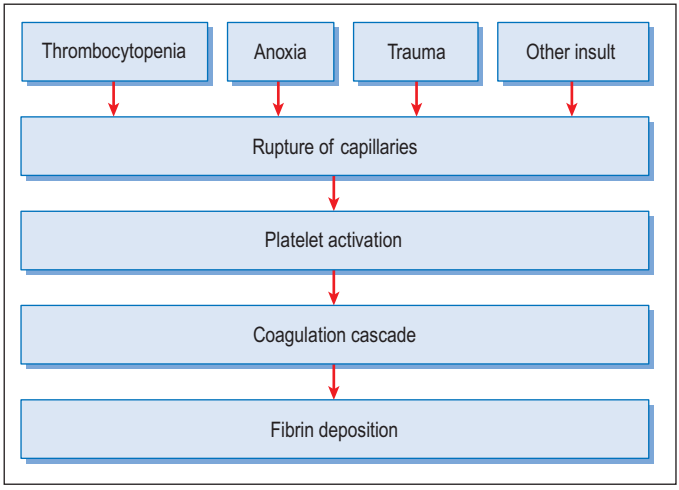

FIGURE 3.35 Roth's spots mechanism

S1 (first heart sound): accentuated

DESCRIPTION

The first heart sound closes with greater than normal intensity.

CONDITION/S ASSOCIATED WITH

- Shortened PR interval[73]
- Mild mitral stenosis
- High cardiac output states

MECHANISM/S

Shortened PR interval

Normally, the leaflets of both the mitral and tricuspid valves have time to drift towards each other before the onset of the ventricular contraction. With a shortened PR interval the leaflets are further apart at the onset of ventricular contraction, thus they 'slam' shut from a wider distance and produce an accentuated S1.

Mild mitral stenosis

In mild mitral stenosis, a longer pressure gradient is formed between atrium and ventricle,[40] keeping the mitral valve leaflets open and wider apart for longer. They are similarly slammed shut from a distance at the onset of ventricular systole.

High cardiac output states

In high cardiac output states (e.g. tachycardia due to anaemia), diastole is shortened and the tricuspid and mitral valve leaflets close from wider than normal positions.

Sign value

There are limited studies on the value of an accentuated S1.

S1 (first heart sound): diminished

DESCRIPTION

A softer than normal first heart sound.

CONDITION/S ASSOCIATED WITH

- Lengthened PR interval (e.g. first-degree heart block)
- Mitral regurgitation
- Severe mitral stenosis
- Left ventricle with reduced compliance

MECHANISM/S

Lengthened PR interval

A longer PR interval allows more time between atrial contraction and ventricular contraction for the valvular leaflets to drift back towards each other; therefore, when the ventricle does contract, the leaflets are already closer together and less sound is produced.

Mitral regurgitation

In mitral regurgitation, the regurgitant jet prevents the leaflets from completely closing together, diminishing the S1 sound.

Severe mitral stenosis

In severe mitral stenosis, the leaflets are too stiff and fixed to move into either an open or a closed position.

Left ventricle with reduced compliance

In a less compliant ventricle, the end-diastolic pressure is higher, which increases the speed at which the leaflets move back together. When the ventricle contracts to slam the valve shut, the leaflets are already closer together and produce less sound.[73]

S3 (third heart sound)

DESCRIPTION

An audible, dull, low-frequency extra heart sound heard in the rapid filling phase of early diastole. The cadence of the heart sounds in a patient with an S3 is said to be similar to the word 'Kentucky'.

CONDITION/S ASSOCIATED WITH

More common

- Often physiological in young patients (under the age of 40)
- Any cause of ventricular dysfunction may produce a third heart sound

Less common

- Other pathological causes: anaemia, thyrotoxicosis, mitral regurgitation, HOCM, aortic and tricuspid regurgitation

MECHANISM/S

An abrupt limitation of left ventricular inflow during early diastole causes vibration of the entire heart and its blood, resulting in the S3.[104] Typically, this is seen in patients who have increased or exaggerated filling, increased volume status and a stiff, non-compliant ventricle.

SIGN VALUE

An audible third heart sound is a useful sign for left ventricular dysfunction; it is associated with systolic and diastolic dysfunction and has been shown to have negative prognostic value in patients with heart failure.

It has been shown to predict systolic dysfunction or ejection fraction of less than 50% with 51% sensitivity and 90% specificity. There is good evidence for its value in predicting elevated left ventricular pressure (>15 mmHg) with sensitivity of 41% and specificity of 92%, with a PPV of 81 and NPV of 65.[105]

S4 (fourth heart sound)

DESCRIPTION

The fourth heart sound is sound heard in addition to the normal S1 and S2. It is usually described as a low-pitched sound heard in late diastole with the onset of atrial contraction. This is different to the S3 or third heart sound, which is heard early in diastole.

CONDITION/S ASSOCIATED WITH

An S4 is typically found in conditions that cause a decrease in compliance of the left ventricle or diastolic dysfunction. Any condition causing stiffening of the left ventricle may cause an S4.

Common

- Hypertension with left ventricular hypertrophy
- Aortic stenosis
- Hypertrophic cardiomyopathy
- Ischaemic changes
- Advancing age

Less common

An S4 can also be heard in conditions where there is a rapid inflow of blood, such as anaemia (owing to a high output state) and mitral regurgitation.

MECHANISM/S

Forceful contraction of the atrium pushes blood into a non-compliant left ventricle. The sudden deceleration of blood against the stiff ventricular wall produces a low-frequency vibration, recognised as the fourth heart sound.

SIGN VALUE

Evidence on the usefulness of an S4 is inconsistent. Some studies[105–107] have shown an association between a stiffened left ventricle and S4 being a pathological finding. Others did not find a valuable relationship between diastolic dysfunction and the presence of a fourth heart sound,[108] labelling it a non-specific and non-sensitive finding.

By phonographic recording, studies have shown a fourth heart sound to be present in 30–87% of heart disease patients but also in 55–75% of people without heart disease.[109–116]

Splinter haemorrhages

DESCRIPTION

Small, red-brown lines of blood seen beneath the nails. They run in line with the nail and have the appearance of splinters caught underneath the nail.

CONDITION/S ASSOCIATED WITH

- Bacterial endocarditis
- Trauma
- Scleroderma
- SLE

MECHANISM/S

In bacterial endocarditis, this sign is thought to be caused by emboli creating clots in capillaries under the nail, resulting in haemorrhage.

SIGN VALUE

Splinter haemorrhages are seen in only up to 15% of cases[84] of bacterial endocarditis and, therefore, have a low sensitivity. Like the other 'classic' eponymous signs of bacterial endocarditis, they are of limited value in isolation from other signs and symptoms.

For other signs of bacterial endocarditis, see 'Janeway lesions', 'Osler's nodes' and 'Roth's spots' in this chapter.

Splitting heart sounds

Splitting of the heart sounds usually refers to the second heart sound or S2 (closure of pulmonary and aortic valves). Different types of split are caused by different physiologies and pathologies.

Splitting heart sounds: paradoxical (reverse) splitting

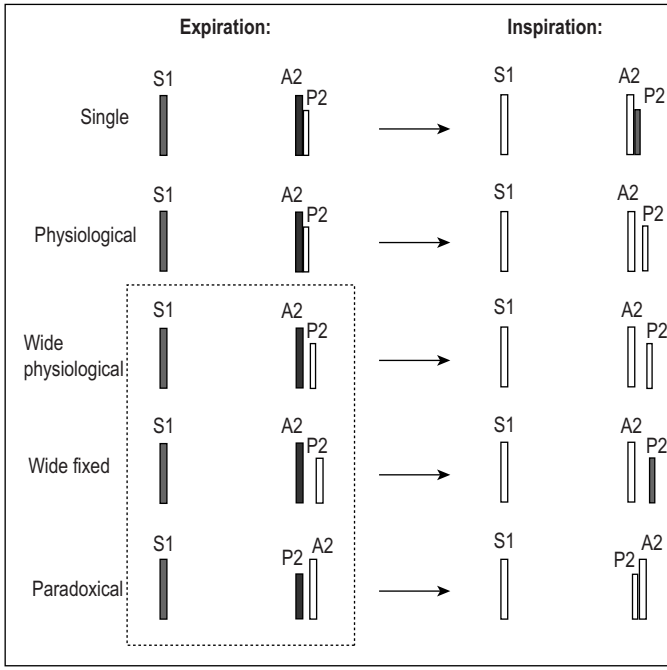

FIGURE 3.36
Paradoxical/reverse splitting of heart sounds

Based on McGee S, *Evidence-Based Physical Diagnosis*, 2nd edn, St Louis: Science Direct, 2007: Fig 36.1.

DESCRIPTION

Essentially the opposite of physiological splitting, paradoxical splitting refers to the situation in which the splitting of the heart sounds disappears on inspiration and there is an audible splitting of A2 and P2 on expiration.

CONDITION/S ASSOCIATED WITH

- Left bundle branch block (LBBB)
- Aortic stenosis

MECHANISM/S

Delaying of A2 is the final pathway for most causes of paradoxical splitting.

Aortic stenosis

In aortic stenosis, the valve becomes so stiffened and closes so slowly that it is heard after the pulmonary valve.

LBBB

In LBBB the delayed depolarisation of the left ventricle causes outflow from the left ventricle to occur later and valvular closure to occur after P2.

SIGN VALUE

In the setting of aortic stenosis, it is of limited value as it only has moderate sensitivity (50%) and specificity (79%) for aortic stenosis and does not distinguish between severe aortic stenosis and minor aortic stenosis.[27] There are few studies of the value of paradoxical splitting in LBBB.

Splitting heart sounds: physiological splitting

DESCRIPTION

Hearing the aortic valve and pulmonary valve closing distinctly and separately during inspiration. They are both high-pitched sounds heard best in the pulmonary area of the praecordium.

CONDITION/S ASSOCIATED WITH

None, it is physiological.

MECHANISM/S

The key to this sign is the pulmonary component of the second heart sound (P2) being delayed and/or closure of the aortic component of the second heart sound (A2) occurring slightly earlier than normal.

On inspiration, intrathoracic pressure becomes more negative and the lungs expand. Lung expansion decreases resistance in the pulmonary vasculature and increases capacitance (the amount of blood in the vessels of the lungs). In addition, because of the low resistance, blood flow through the pulmonary valve continues after systole (this is known as 'hangout'). As a consequence, there is a transient drop in the back pressure from the lungs into the pulmonary artery that is responsible for P2 closure – so the P2 occurs later.

In addition, as the lungs expand and capacitance of the lungs increases, there is a temporary drop-off in blood volume returning to the left atrium and ventricle. This reduction in filling means the next systolic contraction will have a slightly smaller stroke volume and, therefore, the left ventricle will empty faster and the aortic valve (A2) will close earlier.

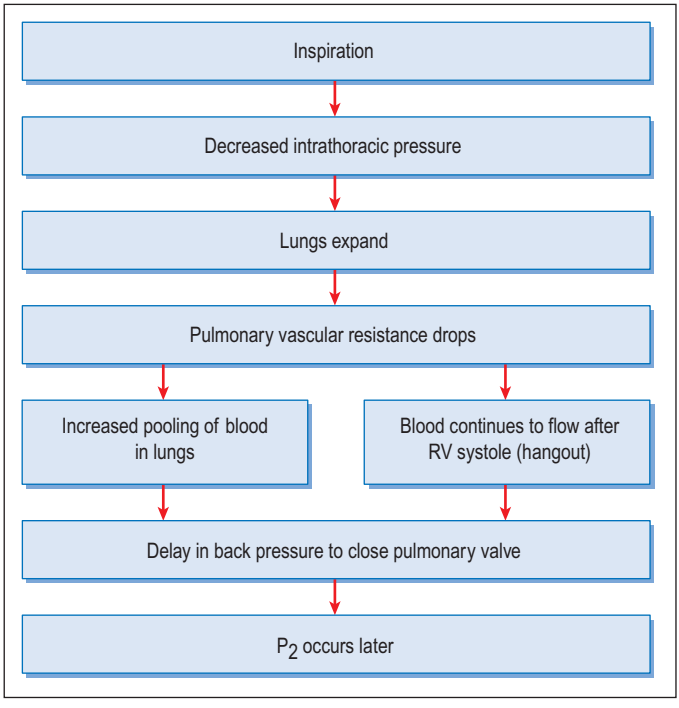

FIGURE 3.37 Mechanisms of physiological splitting

Splitting heart sounds: widened splitting

DESCRIPTION

Refers to a situation in which A2 and P2 are split during expiration, and the timing of the split is even wider than normal during inspiration.

CONDITION/S ASSOCIATED WITH

- Right bundle branch block (RBBB)
- Pulmonary stenosis

MECHANISM/S

In theory, a widened split comes down to either what can make the pulmonary valve close later or what can make the aortic value close earlier.

Pulmonary stenosis

In pulmonary stenosis, the pulmonary valve is damaged and stiffened so that it is slower to close after right ventricular emptying.

Right bundle branch block (RBBB)

In RBBB the delayed depolarisation leads to delayed right ventricular contraction and ejection. The closure of the pulmonary valve is therefore delayed as well.

Splitting heart sounds: widened splitting – fixed

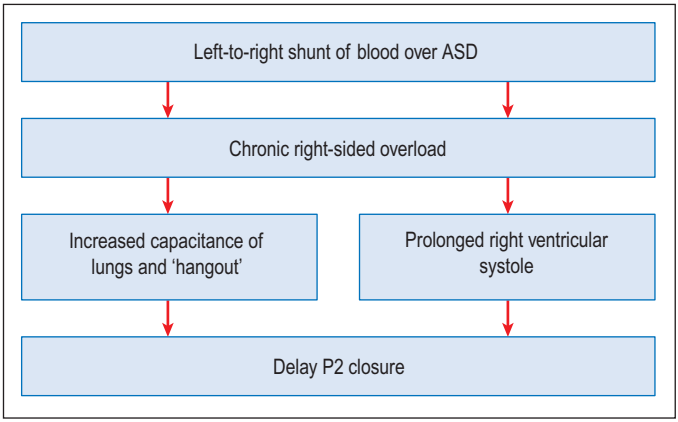

FIGURE 3.38
Mechanisms of widened fixed splitting of heart sounds

DESCRIPTION

Fixed splitting of S2 refers to the situation in which the time between A2 and P2 remains consistently widened throughout the inspiratory/expiratory cycle.

CONDITION/S ASSOCIATED WITH

- Atrial septal defect (ASD)

MECHANISM/S

An ASD allows blood to flow from the left heart to the right heart circulation, causing chronic right-sided volume overload. This overload leads to a high capacitance (the lungs hold more blood), low resistance in the pulmonary system and, therefore, less pulmonary artery pressure on the pulmonary valve. In addition, because of the volume overload it is thought that the right ventricle takes longer to expel blood and, hence, the pulmonary valve closes later than normal.

The reason it is 'fixed' is related to two factors. Firstly, inspiration cannot substantially increase the already raised vascular capacitance of the lungs and, secondly, the naturally occurring increased venous return to the right atrium on inspiration is offset by the blood being shunted from left to right across the ASD.[73]

SIGN VALUE

Fixed splitting has high sensitivity (92%) but lower specificity (65%) for the presence of an ASD.[117] If it is absent, it is unlikely that an ASD is present.

Tachycardia (sinus)

DESCRIPTION

A regular heart rate of more than 100 beats per minute.

CONDITION/S ASSOCIATED WITH

Sinus tachycardia is associated with a number of conditions. These may be normal physiological responses or a reaction to a pathological insult. The conditions include, but are not limited to:

More common

- Exercise
- Anxiety
- Pain
- Fever/infection
- Hypovolaemia
- Anaemia
- Decreased cardiac output (e.g. heart failure)
- Sino-atrial node dysfunction
- Pulmonary embolism
- Hyperthyroidism
- Stimulants and drugs (e.g. caffeine, beta-2 agonists, cocaine)
- Hypoxia
- Myocardial infarction

Less common

- Phaeochromocytoma

MECHANISM/S

Knowing the mechanism for each cause of tachycardia is impractical. For most causes the final common pathway for the development of sinus tachycardia is activation of the sympathetic nervous system and/or catecholamine release. This can be appropriate in the case of anxiety, fear or hypovolaemia, or inappropriate in the case of a phaeochromocytoma or drugs that release (or cause the release of) catecholamines.

Mechanism in hyperthyroidism

The mechanism of tachycardia in hyperthyroidism is unique and is a result of *increased T3 levels*.

T3 has genomic (induction and expression of specific genes) and non-genomic properties that influence the production and alter the performance of myofibrillary proteins, sarcoplasmic reticula, ATPases and sodium, potassium and calcium channels. The end result is increased contractility and increased heart rate and cardiac output.[118]

SIGN VALUE

Isolated tachycardia is a very non-specific sign. Its value as a clinical sign is dependent on clinical context. However, studies have shown the following:

- It has limited independent value in predicting hypovolaemia.[119]
- In conjunction with other variables, it has value in predicting pneumonia.[120]
- In trauma, sepsis pneumonia and myocardial infarction, tachycardia has been shown to have prognostic value in predicting increased risk of mortality.[121–125]

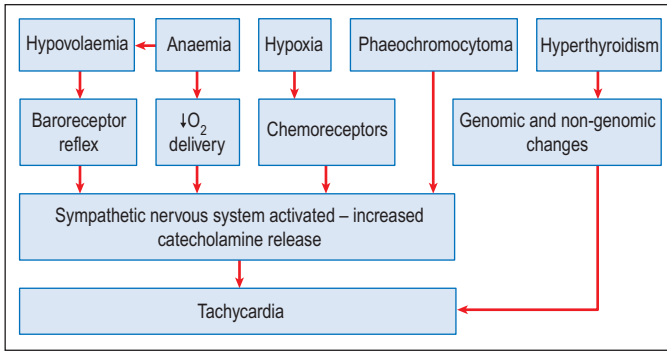

FIGURE 3.39 Mechanisms of tachycardia

Xanthelasmata

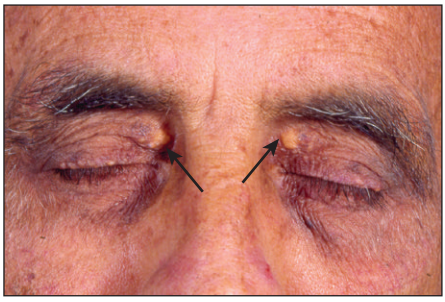

FIGURE 3.40 Xanthelasmata

Reproduced, with permission, from Rakel RE, *Textbook of Family Medicine*, 7th edn, Philadelphia: Saunders, 2007: Fig 44-66.

DESCRIPTION

Well demarcated, yellow plaques of cholesterol most often seen around eyes.

CONDITION/S ASSOCIATED WITH

- Hypercholesterolaemia (although only 50% of people with xanthelasmata are actually hyperlipidaemic)[126]
- Diabetes
- Fredrickson hyperlipidaemia
- Primary biliary cirrhosis

MECHANISM/S

Patients with xanthelasmata have been found to have lipid abnormalities – higher-than-normal LDL and lower-than-normal HDL. However, the mechanism/s involved may vary, depending on whether the patient is normolipidaemic or hyperlipidaemic.

Hyperlipidaemic

In hyperlipidaemic patients with xanthelasmata, elevated cholesterol, mostly of the LDL type, enters through capillary walls to form the skin lesion.

Normolipidaemic

The mechanisms are less clear but those postulated include:[117,126,127]

- Local trauma and inflammation are thought to alter vascular permeability, allowing lipoproteins to enter the dermis and subsequently be taken up by dermal cells.
- Dermal macrophages, which are not regulated by the body's normal mechanisms (which limit cellular uptake of LDL cholesterol), take up cholesterol and become foam cells, which deposit themselves in the dermal layer.
- HDL, which normally removes excess cholesterol from tissues, is low in many patients with xanthelasmata; therefore, less cholesterol is being removed from the tissues and a build-up occurs.

SIGN VALUE

The value of xanthelasmata as a sign and predictor of disease is still being clarified. However, a brief summary of what is known includes:

- The prevalence of atherosclerosis in patients with xanthelasmata has varied between 15% and 69% in different studies.
- Recent studies[127–129] have shown an increased risk of ischaemic heart disease for men over 50. There was no increase in risk of heart disease shown for women, and no association with peripheral vascular disease was found in these studies.
- Patients who are hyperlipidaemic and have xanthelasmata have an increased risk of cardiovascular disease, and management should be based on cholesterol and lipoprotein abnormalities.
- In patients who are normolipidaemic, the significance of xanthelasmata is less clear, as there is a lack of sound studies and some data are conflicting.

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CHAPTER 4

Haematological/ Oncological Signs

Angular stomatitis

DESCRIPTION

Maculopapular and vesicular lesions grouped on the skin at the corners (or 'angles') of the mouth and the mucocutaneous junction.

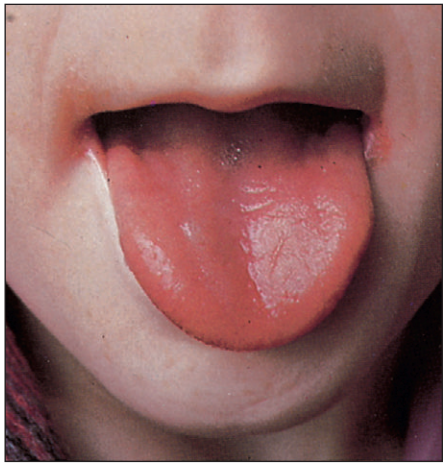

FIGURE 4.1 Angular stomatitis

(Note atrophic glossitis is also present.)

Reproduced, with permission, from Forbes CD, Jackson WF, *Color Atlas and Text of Clinical Medicine*, 3rd edn, London: Mosby, 2003.

CONDITION/S ASSOCIATED WITH

More common

- Oral candidiasis
- Poorly fitting dentures
- Bacterial infection

Less common

- Nutritional deficiencies (especially riboflavin, iron and pyridoxine)
- Human immunodeficiency virus (HIV)

NUTRITIONAL DEFICIENCY MECHANISM/S

Iron and other nutrients are necessary in gene transcription for essential cell replication, repair and protection. Nutrient deficiency leads to impeded protection, repair and replacement of the epithelial cells on the edges of the mouth, resulting in atrophic stomatitis.

SIGN VALUE

Limited clear evidence on the value of angular stomatitis as a sign.

Atrophic glossitis

DESCRIPTION

The absence or flattening of the filiform papillae of the tongue.[1] See Figure 4.1.

CONDITION/S ASSOCIATED WITH

More common

Associated with micronutrient deficiency, including:

- Iron deficiency
- Vitamin B12 deficiency
- Folic acid deficiency
- Thiamine deficiency
- Niacin deficiency
- Vitamin E deficiency

Less common

- Amyloidosis
- Sjögren's syndrome

MECHANISM/S

It is thought that micronutrient deficiency impedes mucosal proliferation.

As cells of the tongue papillae have a high rate of turnover, deficiencies in micronutrients needed for cell proliferation or cell membrane stabilisation may lead to depapillation.[2]

Nutritional deficiency is also thought to change the pattern of microbial flora, thus contributing to glossitis.[3]

SIGN VALUE

Although still limited, there is some growing evidence that atrophic glossitis is a marker for malnutrition and decreased muscle function.[1] In one larger-scale study,[1] atrophic glossitis was found in 13.2% of men and 5.6% of women at home and in 26.6% of men and 37% of women in hospital. It was also further correlated with decreased weight, decreased BMI, poor anthropometry measurements and decreased vitamin B12.

Other smaller case reports[2,4] have also found it useful in identifying micronutrient deficiencies.

Bone tenderness/bone pain

DESCRIPTION

Pain in any part of the skeletal system. Pain may be present with or without palpation.

CONDITION/S ASSOCIATED WITH

Many different malignancies may cause bone pain.

More common

- Prostate cancer
- Breast cancer
- Multiple myeloma
- Hodgkin's and non-Hodgkin's lymphoma
- Lung cancer
- Ovarian cancer

GENERAL MECHANISM/S

The mechanism is very complex.

Key factors that contribute to the development of cancer-induced bone pain include:

1. *complication of direct malignant invasion*
2. malignancy-induced *osteoclast/osteoblast imbalance*
3. *alteration of the normal pain pathways*.

Complication of direct malignant invasion

As tumour cells invade normal tissue and bone, they destroy normal architecture. In doing so they can cause nerve damage, vascular occlusion and/or distension of the pain-sensitive periosteum – all of which will stimulate nerve afferents and produce pain.[5–7]

Malignancy-induced osteoclast/osteoblast imbalance

Malignancy, whether it is primary or metastatic, has been shown to change the osteoblastic/osteoclastic balance. This results in either lytic lesions or abnormally weakened bone that is subject to microfractures.

Increased bone turnover may also produce pain, similar to the 'growing pains' of rapid bone growth in adolescence.

The mechanism of the osteoclast/osteoblast imbalance/pain can be the result of several factors:

1. Paracrine secretion of endothelin 1 and parathyroid hormone-related protein (PTH-rp) increases osteoclastic activity.
2. 'Cross-talk' from malignant cells to orthoclastic cells results in increased osteoclast activity.[8]
3. In the destruction of bone matrix, more growth factors are released, which in turn increases cell proliferation and, ultimately, tumour burden.
4. Inflammation and release of cytokines tumour necrosis factor (TNF) and interleukins (IL-1 and IL-6), prostanoids that activate pain fibres.[5,6,9]
5. Alteration of the receptor activator of nuclear factor kappa (RANK) pathway[6] – RANK is a receptor activator expressed on osteoclasts. RANK ligand (RANK-L) is expressed on a number of cell types including osteoblasts. The RANK to RANK-L

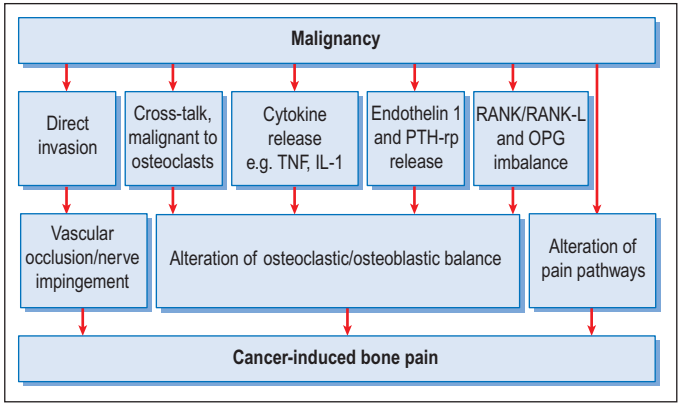

FIGURE 4.2 Mechanisms of cancer-induced bone pain

interaction is central to maintaining a normal activation of osteoclasts.[6]

In cancer, activated T cells and cancer cells secrete RANK-L and sequester OPG (a cytokine that limits osteoclast activity), resulting in more osteoclast activation.

6 WNT (wingless-type) pathway – recent research has unearthed a new family of glycoproteins that influence the bone formation and resorption[10] process directly and via some of the mechanisms above. Its exact influence in cancer-induced bone pain is still to be elicited.

Alteration of normal pain pathways

Studies have shown that metastatic malignancies in bone can cause alterations within the pain pathway.[5,6,11] These changes lower the pain threshold and increase the likelihood for a pain impulse to be sent.

Changes in the CNS and pain pathways in bone malignancy that have been demonstrated include:

1 reorganisation of the dorsal horn and sensitisation of pain afferents to substance P (which stimulates pain pathways)[8,9]
2 astrocyte hypertrophy[6] and decreased glutamate reuptake transporters, causing increased glutamate and excitotoxicity[8,9]
3 an increase in certain glial proteins found in the spinal cord that serve to increase the transmission of pain[8]
4 the acidic environment produced by osteoclasts may stimulate pain receptors.[5,9]

SIGN VALUE

New-onset bone pain is an important sign to recognise in both the cancer-naïve patient and those with a known diagnosis. Bone pain is the most frequent complication of metastatic bone disease,[12,13] being reported in 50–90% of patients with skeletal metastases and in 70–95% of patients with multiple myeloma. Indeed, in patients with underlying metastases, bone pain or bony tenderness may be the first complaint described, especially in the case of multiple myeloma.

Chipmunk facies

DESCRIPTION

Abnormality of the craniofacial bones resulting in prominent frontal and parietal bones, depressed nasal bridge and protruding upper teeth (similar to those of a chipmunk).

CONDITION/S ASSOCIATED WITH

- Beta thalassaemia
- Parotid gland enlargement

BETA THALASSAEMIA MECHANISM/S

Extramedullary haematopoiesis (EMH) is the cause.

In beta thalassaemia, there is abnormal production of normal beta chains of haemoglobin (Hb), which results in abnormal Hb. This leads to decreased Hb synthesis and increased red blood cell destruction. In order to compensate for the reduced Hb, the bone marrow (where Hb is normally made) increases activity (hyperplasia) and haematopoiesis occurs outside the bone marrow (EMH).[14]

This EMH affects certain bones more than others, and the marrow activity in these bones causes deformities that produce the facies.

EXTRAMEDULLARY HAEMATOPOIESIS, AN ABNORMAL BIRTHPLACE OF CELLS

Extramedullary haematopoiesis (EMH) is the birth and production of cells outside the bone marrow.

It is an unusual irregularity that is most commonly seen in disorders that lead to the destruction of the normal bone marrow, including myelofibrosis, myeloproliferative disorders and infiltrating tumours, or in situations where the marrow cannot keep up with the demand for new cells (e.g. haemoglobinopathies).

Common sites of EMH include: liver, spleen, adrenal glands, kidneys and lymph nodes[15] but it has also been seen in a number of other locations, including the epidural space, bones, synovium, dermis, pleura and paraverterbal and retroperitoneal spaces.

The cause of it is unclear. It is thought to be a compensatory response to conditions that cause inadequate production of cells through either destruction of the bone marrow or increased production requirement. It may originate from the release of stem cells from the bone marrow into the circulation.[16]

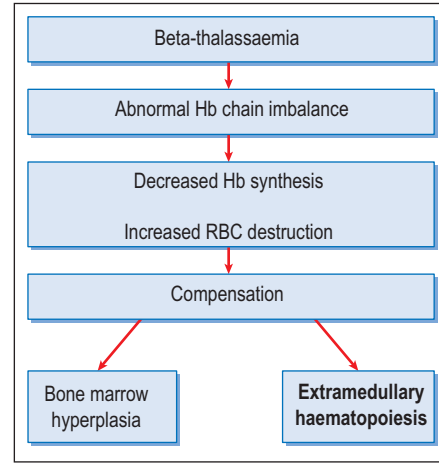

FIGURE 4.3 Extramedullary haematopoeisis

Based on Swanson TA, Kim SI, Flomin OE, *Underground Clinical Vignettes Step 1: Pathophysiology I, Pulmonary, Ob/Gyn, ENT, Hem/Onc*, 5th edn, Lippincott, Williams & Wilkins, 2007; Fig 95-1.

Conjunctival pallor

DESCRIPTION

When the lower eyelid is pulled down for inspection, the mucosal surface of the inner eyelid is seen to be whiter or paler than the normal pink-red of health.

CONDITION/S ASSOCIATED WITH

- Anaemia

MECHANISM/S

In anaemia there is a deficiency of oxyhaemoglobin (which gives blood its normal red colour). Hence, capillaries and venules appear pale, as does the conjunctiva.

SIGN VALUE

A number of studies have appraised the validity of conjunctival pallor in the assessment of anaemia. It has some value as a sign with sensitivity of 25–62% and specificity of 82–97% and PLR of 4.7.[17–21]

Ecchymoses, purpura and petechiae

DESCRIPTION

Ecchymoses, purpura and petechiae all refer to subcutaneous haematomas of diverse sizes. It is important to remember that one condition can cause a range of differently sized stigmata. That is, a petechiae-causing pathology may also cause ecchymoses. In reality, the causes will often overlap (see Table 4.1), and it is important to have a basic understanding of the general mechanisms rather than the numerous disorders leading to them.

GENERAL MECHANISM/S

A subcutaneous haematoma of any size can be the result of a disruption of:

1. the *blood vessel wall*
2. the *normal coagulation/clotting process*
3. the *number or function of platelets*.

The resultant bleeding under the skin (with haemoglobin providing the initial red/blue colour) is then further classified by size.

Thrombocytopenia

A significant enough thrombocytopenia will result in inadequate control and clotting of any bleed because of a lack of platelet activation and platelet 'plugging'. Trauma from any cause, no matter how minor, may precipitate mucocutaneous bleeding and, without adequate clotting, petechiae, purpura or ecchymoses may occur before the bleed is controlled.

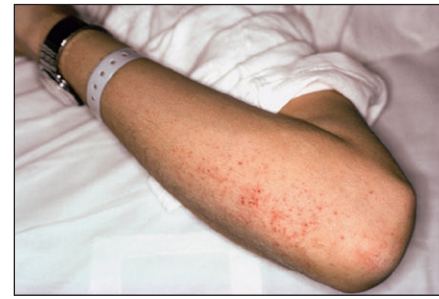

FIGURE 4.4 Petechiae in a patient with thrombocytopenia

Reproduced, with permission, from Little JW, Falace DA, Miller CS, Rhodus NL, *Dental Management of the Medically Compromised Patient*, 7th edn, St Louis: Mosby Elsevier, 2008: Fig 25-9.

TABLE 4.1 Causes of petechiae, purpura and ecchymoses

Petechiae	Purpura	Ecchymoses
DESCRIPTION		
Small (1–2 mm) haemorrhages into mucosal or serosal surfaces	>3 mm haemorrhages, or when ecchymoses and petechiae form in groups[22]	Subcutaneous haematoma >10–20 mm
CONDITION/S ASSOCIATED WITH		
Thrombocytopenia of any cause (e.g. autoimmune, heparin-induced, hypersplenism) Bone marrow failure (e.g. malignancy) Defective platelet function (rare) (e.g. Glanzmann's thromboasthenia uraemia) Disseminated intravascular coagulation Infection Bone marrow defects Factor deficiencies	Diseases associated with: As for petechiae: Trauma Vasculitis – particularly *palpable purpura* Amyloidosis Over-anticoagulation Factor deficiencies	As for petechiae and purpura: Trauma – common Diseases causing: Defective platelet action Vasculitis – *palpable purpura* Amyloidosis Hereditary haemorrhagic telangiectasia Scurvy Cushing's syndrome Over-anticoagulation Factor deficiencies (e.g. haemophilia)

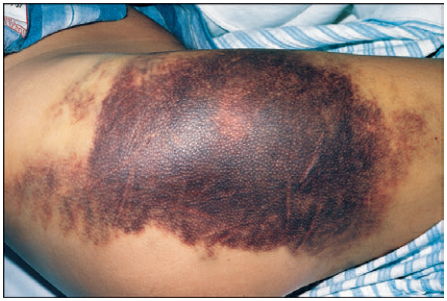

FIGURE 4.5 Ecchymoses in a patient with haemophilia

Reproduced, with permission, from Little JW, Falace DA, Miller CS, Rhodus NL, *Dental Management of the Medically Compromised Patient*, 7th edn, St Louis: Mosby Elsevier, 2008: Fig 25-16.

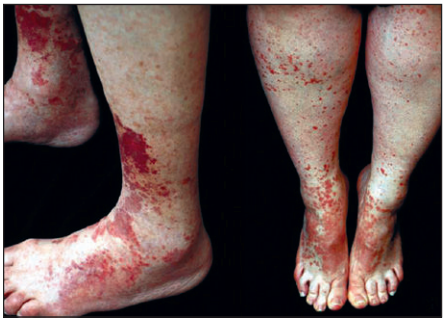

FIGURE 4.6 Palpable purpura

In a patient with Henoch–Schönlein purpura (left) and hepatitis C and cryoglobulinaemia (right).

Reproduced, with permission, from Libby P, Bonow R, Zipes R, Mann D, *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 8th edn, Philadelphia: Saunders, 2007: Fig 84-1.

Vasculitis

Inflammation of the small arterioles or venules in the skin, associated with immune complex deposition, produces inflammation with punctate oedema and haemorrhage and, thus, palpable purpura.[22]

Cushing's

Ecchymoses in Cushing's syndrome are thought to be related to a lack of connective tissue support in vessel walls, owing to corticosteroid-induced reduction in collagen synthesis.[23]

Mechanism of colour changes

Once under the skin, erythrocytes are phagocytosed and degraded by macrophages, with haemoglobin converted to bilirubin providing the blue–green colour. Bilirubin is eventually broken down into haemosiderin (golden brown colour) at the end of the process before skin returns to its normal colour.

SIGN VALUE

Although there is limited evidence for the value of petechiae, ecchymoses and purpura as clinical signs and the specificity is low, given the numerous potential causes, normal healthy patients rarely produce these signs and therefore they should be investigated if seen.

Gum hypertrophy (gingival hyperplasia)

DESCRIPTION

Excessive growth or expansion of the gingival tissue

CONDITION/S ASSOCIATED WITH

- Leukaemia
- Drug-induced (e.g. phenytoin, cyclosporin)

LEUKAEMIA MECHANISM/S

Thought to be due to the invasion of leukaemic cells into the gingival tissues.[24]

DRUG-INDUCED MECHANISM/S

The mechanism is unclear. There is thought to be an interaction between the offending drug and epithelial keratinocytes, fibroblasts and collagen, causing an overgrowth of tissue in susceptible individuals.[25]

Phenytoin has been shown to be interactive with a group of sensitive fibroblasts, whereas cyclosporin may affect the metabolic function of fibroblasts. A cofactor (e.g. inflammation) may be required to be present in order for the sign to occur.

SIGN VALUE

A relatively uncommon sign, seen mostly in acute myelogenous leukaemia, but even so only in about 3–5% of cases.[26]

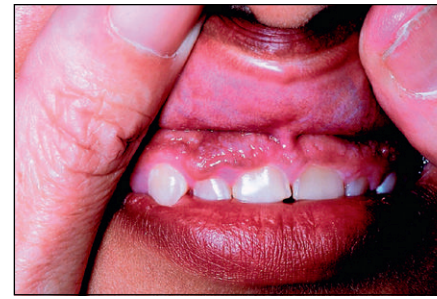

FIGURE 4.7 Gum hypertrophy

Reproduced, with permission, from Sidwell RU et al, *J Am Acad Dermatol* 2004; 50(2, Suppl 1): 53–56.

Haemolytic/pre-hepatic jaundice

DESCRIPTION

Yellowing of the skin, sclera and mucous membranes.

CONDITION/S ASSOCIATED WITH

The causes of haemolytic or pre-hepatic jaundice can be grouped in a number of ways, one of which is whether breakdown is due to intrinsic or extrinsic factors (Table 4.2).

GENERAL MECHANISM/S

The common end point in the development of jaundice is a build-up of *excess bilirubin, which is then deposited in the skin and mucous membranes*. Jaundice is not clinically evident until bilirubin exceeds 3 mg/L.

In pre-hepatic jaundice, *red blood cell (RBC) destruction causes excess haem* to be released, which is then passed on to the liver to be metabolised. The amount of haem released is such that the liver is overwhelmed and unable to conjugate and excrete all the bilirubin, leading to hyperbilirubinaemia and jaundice.

Destruction

A summary of examples of how RBCs are destroyed in specific disorders (leading to the release of bilirubin that builds up to cause jaundice) is shown in Table 4.3.

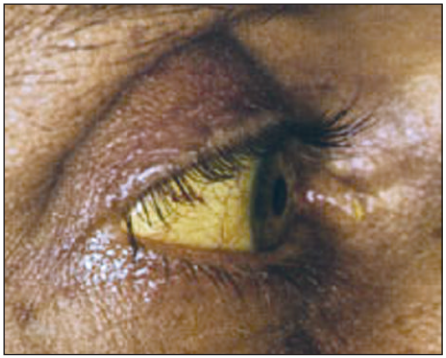

FIGURE 4.8 Jaundice with scleral icterus

Reproduced, with permission, from Stern TA, Rosenbaum JF, Fava M, Biederman J, Rauch SL, *Massachusetts General Hospital Comprehensive Clinical Psychiatry*, 1st edn, Philadelphia: Mosby, 2008: Fig 21-17.

TABLE 4.2 Classification of autoimmune haemolytic anaemia

Warm antibody type	Cold antibody type
IDIOPATHIC	IDIOPATHIC (COLD HAEMAGGLUTININ DISEASE, CHAD)
Secondary • Other autoimmune disorders (e.g. systemic lupus erythematosus) • Lymphoma, chronic lymphocytic leukaemia • Drugs (e.g. methyldopa fludarabine) • Post stem cell transplantation	Secondary • Infections (e.g. *Mycoplasma pneumoniae*, infectious mononucleosis) • Paroxysmal cold haemoglobinuria

TABLE 4.3 Factors causing destruction of RBCs leading to jaundice

Factor	Mechanism
Hereditary spherocytosis	Genetic abnormality – fragile irregular-shaped RBCs – unable to pass through splenic circulation – spleen removes and destroys
Glucose-6-phosphate dehydrogenase (G6PD) deficiency	Lack of anti-oxidative enzyme – RBCs susceptible to stress (e.g. hypoxia, foods) – oxidative stress destroys RBCs
Sickle cell anaemia	Abnormal haemoglobin – RBCs stick and clump together and are more fragile – increased cell stress and breakdown occurs
Immune	Antibodies (either primary or secondary to autoimmune disorder or malignancy) attack RBCs and cause destruction
Microangiopathic	Fibrin strands deposited in small vessels – shearing of RBCs as they pass through the circulation
Malaria	Parasitic invasion of RBCs – destruction of RBCs
Haemolytic disease of newborn	Maternal antibodies cross placenta and attack fetal RBCs

SIGN VALUE

Jaundice is pathological and requires diagnostic work-up. For a review of other causes of jaundice, see Chapter 6, 'Gastroenterological signs'.

Koilonychia

DESCRIPTION

Described as the loss of longitudinal and lateral convexity of the nail, with thinning and fraying of the distal portion. Or put simply – spoon-shaped nails.

CONDITION/S ASSOCIATED WITH

More common

- Physiological variant of normal
- Soft nails with occupational damage

Less common

- Iron deficiency anaemia
- Haemochromatosis – rare
- Raynaud's syndrome

MECHANISM/S

The exact mechanism is not known. Koilonychia is associated with a soft nail bed and matrix, but why this occurs is unclear.[27]

SIGN VALUE

There is little evidence on koilonychia as a sign in iron deficiency anaemia.

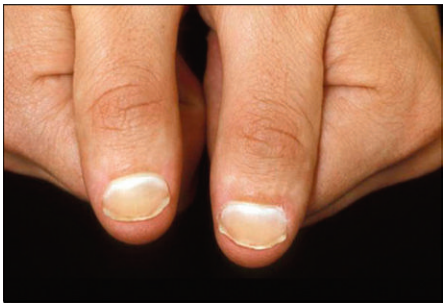

FIGURE 4.9 Koilonychia – spoon-shaped nails

Reproduced, with permission, from Grandinetti LM, Tomecki KJ, Chapter: Nail abnormalities and systemic disease. In: Carey WD, *Cleveland Clinic: Current Clinical Medicine*, 2nd edn, Philadelphia: Saunders, 2010: Fig 4.

Leser–Trélat sign

DESCRIPTION

The sudden onset of large numbers of seborrhoeic keratoses with an associated malignant process.

CONDITION/S ASSOCIATED WITH

More common

- Adenocarcinoma of stomach, liver, pancreas, colorectal
- Breast cancer
- Lung cancer

Less common

- Urinary tract cancers
- Melanoma

MECHANISM/S

Most likely due to the paraneoplastic secretion of *different growth factors*, including epidermal growth factor, growth hormone and transforming growth factor, which *alter the extracellular matrix and promote seborrhoeic keratoses*.[28,29]

SIGN VALUE

The value of Leser–Trélat sign in internal malignancies is controversial. Some studies[28] suggest that the association is coincidental, and one review[29] finds it of limited use. However, there are few formal studies to clarify the picture.

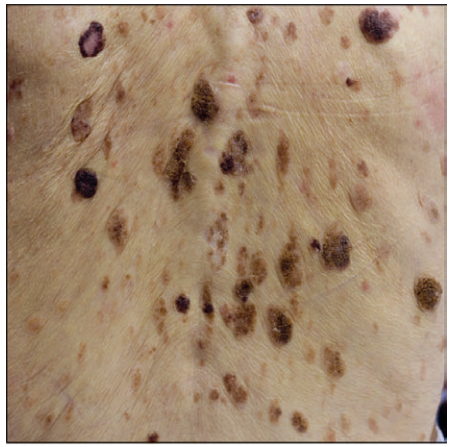

FIGURE 4.10 Leser–Trélat sign

Reproduced, with permission, from Ho ML, Girardi PA, Williams D, Lord RVN, J Gastroenterol Hepatol 2008; 23(4): 672.

Leucoplakia

DESCRIPTION

A fixed white lesion in the oral cavity that is not removed by rubbing and does not disappear spontaneously.

CONDITION/S ASSOCIATED WITH

Squamous cell carcinoma (SCC) of the head or neck.

MECHANISM/S

The reason for the development of leucoplakia is not clear.

It is often described as a *pre-malignant lesion* with some features of dysplasia. Risk factors for leucoplakia include cigarette smoking and cigarette products, *Candida* infection, previous malignancy or pre-malignancy and human papilloma virus (HPV).[30] It is assumed that all of these risk factors can somehow cause changes in the DNA and/or tumour suppressor genes of cells that result in a disposition to produce cancerous lesions.

SIGN VALUE

The overall prevalence of leucoplakia is approximately 0.2–5%. 2–6% of lesions represent dysplasia or early invasive SCC,[31] and 50% of oral SCCs will present with leucoplakia. It is recommended that all patients diagnosed with leucoplakia be evaluated for cancer.

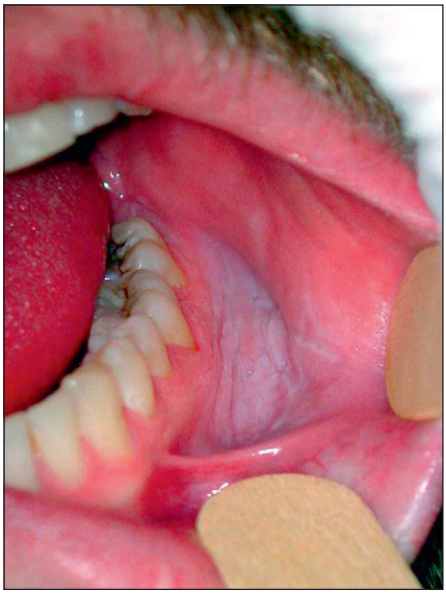

FIGURE 4.11 Leucoplakia

Reproduced, with permission, from World Articles in Ear, Nose and Throat website. Available: http://www.entusa.com/oral_photos.htm [9 Feb 2011].

Lymphadenopathy

DESCRIPTION

Enlarged lymph nodes able to be palpated or seen on certain imaging.

CONDITION/S ASSOCIATED WITH

Hundreds of disorders can present with lymphadenopathy as part of their clinical picture. MIAMI is one useful acronym to help remember the broad causes (see Table 4.4): Malignancy, Infectious, Autoimmune, Miscellaneous and Iatrogenic.[32]

GENERAL MECHANISM/S

In general, most of the conditions that result in lymphadenopathy do so through either:

1. *propagation of an inflammatory response whether it be systemic, regional or direct*[33]
2. *invasion and/or proliferation of abnormal or malignant cells.*[33,34]

Malignancy

Malignancy causes lymphadenopathy through invasion or infiltration of malignant cells *into* the lymph node or direct proliferation of malignant cells *within* the lymph node.

The lymphatic system provides the predominant mechanism for distant metastatic spread of cells for a variety of solid-tumour cancers (e.g. colorectal, ovarian, prostate). Tumour cells move from the main tumour site via the lymphatic system to lymph nodes, where they accumulate and/or proliferate, enlarging the lymph node.

In lymphoma there is an abnormal proliferation of lymphocytes within the lymph node with associated hyperplasia of normal structures producing lymphadenopathy.

Infectious

The lymphatic system is central to the effective functioning of the immune system. Macrophages and other antigen-presenting cells migrate to the lymph nodes, in order to present antigens to T and B cells. On recognition of an antigen, T and B cells proliferate within the lymph node in order to generate an effective immune response. The lymphadenopathy seen with infection (be it local or systemic) can be viewed as an extension of this normal immune response.

In *direct invasion* of the lymph node, an individual lymph node becomes infected with a bacterium or other type of antigen. The resulting immune response results in hyperplasia of the lymph node structures, T and B cell proliferation and infiltration of other immune cells to address the infection. This results in inflammation and swelling of the node and, thus, lymphadenopathy.

TABLE 4.4 Causes of lymphadenopathy

Malignancy	Infectious	Autoimmune	Miscellaneous	Iatrogenic
Lymphoma	Tonsillitis	Sarcoidosis	Kawasaki's disease	Serum sickness
Leukaemia	Epstein–Barr virus	SLE	Sarcoidosis	Medications
Multiple myeloma	Tuberculosis	Rheumatoid arthritis		
Skin cancer	HIV			
Breast cancer	CMV			
	Streptococcal and staphylococcal infection			
	Cat scratch disease			

Based on McGee S, *Evidenced Based Physical Diagnosis*, 2nd edn. St Louis: Elsevier, 2007: Box 24.1; with permission.

In *systemic infections*, reactive hyperplasia may occur. In response to an antigenic (intracellular or extracellular) stimulus that has been brought to the lymph node to be presented to T and B cells, lymphocytes and other cells resident in the node proliferate,[35] producing lymphadenopathy.

Autoimmune

Autoimmune causes of lymphadenopathy are similar to infectious causes of lymphadenopathy, except that the antigen is a self antigen and the inflammatory response is an inappropriate one. B-cell proliferation is often seen within the lymph nodes of patients with rheumatoid arthritis whereas T-cell proliferation is seen in SLE.[35]

SIGN VALUE

With so many potential causes of lymphadenopathy, its specificity as a sign is limited. The main issue for the medical officer is to determine whether it is arising from a malignant cause or something more benign, such as infection.

Several characteristics are said to make a node more suspicious of malignancy. A review[36] of studies regarding these characteristics in the diagnosis of malignancy or serious underlying disease found that the features in Table 4.5 generally had higher specificity than sensitivity. That is, if the characteristic was present, it was suggestive of a serious underlying cause but, if it was not present, malignancy or another serious cause could not be ruled out.

Time course of the development of lymphadenopathy is also used as an indicator of malignancy, with a shorter time course thought to be more likely due to an acute infective cause whereas a longer time course is suggestive of a malignant cause.

In one study of 457 children presenting with lymphadenopathy, in 98.2% of cases acute lymphadenopathy was due to benign causes and malignancies were most often associated with chronic and generalised lymphadenopathy.[37]

Painful versus painless nodes

It is generally taught that painful nodes are more likely to be reactive or related to an inflammatory process than painless nodes, which are more likely to be malignant. However, evidence for this assumption is limited.

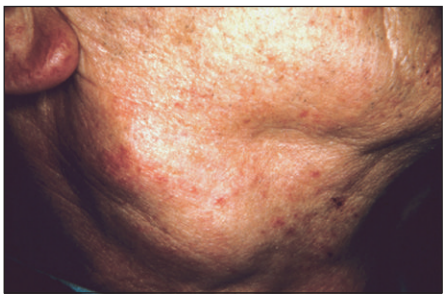

FIGURE 4.12 Cervical lymphadenopathy

Reproduced, with permission, from Little JW, Falace DA, Miller CS, Rhodus NL, *Dental Management of the Medically Compromised Patient*, 7th edn, St Louis: Mosby, 2008: Fig 24-6.

TABLE 4.5 Values of characteristics of lymph nodes in the diagnosis of malignancy or serious underlying disease

Feature	Value
Hard texture	Sensitivity 48–62%, specificity 83–84%, PLR 2.3, NLR 0.6
Fixed lymph nodes	Sensitivity 12–52%, specificity 97%, PLR 10.9
Lymph node size >9 cm^2	Sensitivity 37–38%, specificity 91–98%, PLR 8.4

TABLE 4.6 Drainage areas of lymph nodes

Lymph node	Anatomical drainage area
Cervical	All of the head and neck
Supraclavicular	Thorax, abdominal organs (see Virchow's nodes)
Epitrochlear	Ulnar aspect or arm and hand[42]
Axillary	Ipsilateral arm, breast and chest
Inguinal – horizontal group	Lower anterior wall, lower anal canal
Inguinal – vertical group	Lower limb, penis, scrotum and gluteal area

VIRCHOW'S NODE – GASTROINTESTINAL MALIGNANCY ONLY?

Virchow's node refers to supraclavicular lymphadenopathy and has classically been taught as a sign of gastrointestinal malignancy only, but recent research has shown broader associations.

Mechanism/s

Virchow's node is located at the end of the thoracic duct.[38] Accepted theory is that lymph and malignant cells from the gastrointestinal system travel through the thoracic duct and are deposited in Virchow's node.

Condition/s associated with

Studies[39] have now shown Virchow's node to be present with:

- lung cancer – most common[39]
- pancreatic cancer
- oesophageal cancer
- renal cancer
- ovarian cancer
- testicular cancer[40,41]
- stomach cancer
- prostate cancer
- uterine and cervical cancer
- gallbladder cancer – rare
- liver cancer
- adrenal cancer
- bladder cancer.

LYMPHADENOPATHY: LOCATION – LOCATION – LOCATION

The site of lymphadenopathy may help identify the origin of the underlying conditions. Detailed explanations of the anatomy of the lymph system can be found in any anatomy textbook. The drainage areas associated with various lymph nodes are given in brief in Table 4.6.

Using these anatomical landmarks, clinicians can narrow their search for the primary malignancy.

Generalised lymphadenopathy

Generalised lymphadenopathy is usually described as the enlargement of two or more groups of lymph nodes. It is generally caused by systemic disorders that, by their nature, affect more than just a localised region of the body. Such conditions include lymphoma, leukaemia, tuberculosis, HIV/AIDS, syphilis, other infectious diseases and connective tissue disorders (e.g. rheumatoid arthritis). Although (like anything in medicine) this is not an absolute, it does help the clinician to shorten the differential diagnosis list.

Neoplastic fever

DESCRIPTION

Typically, a diagnosis of exclusion in a patient with cancer, after other possible causes of fever have been ruled out.

CONDITION/S ASSOCIATED WITH

Most forms of cancer.

Differential diagnosis includes other common causes of fever.

MECHANISM/S

The mechanism is not clear.

Suggested theories include:[43]

- pyrogenic cytokines released by cancer cells (e.g. IL-1, IL-6, TNF-alpha and interferon)
- tumour necrosis contributing to release of TNF and other pyrogens
- bone marrow necrosis causing a release of toxins and cytokines from damaged cells.

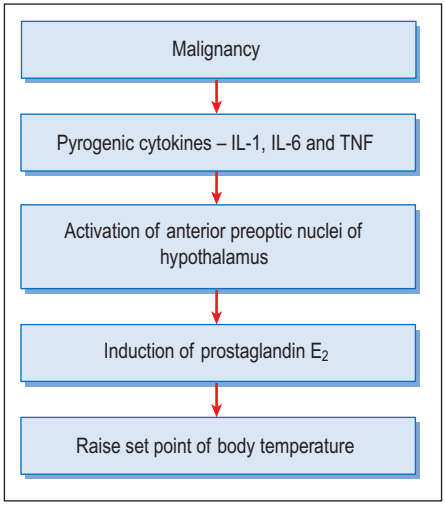

FIGURE 4.13 Neoplastic fever

SIGN VALUE

There is limited information as to its value as a sign. Cancer has been shown to be the cause of fever of unknown origin in 20% of cases.[44]

There is value in identifying neoplastic fever as treatment with NSAIDs (Naproxen) has been shown to alleviate symptoms, unlike the blind use of antibiotics.[43]

Peau d'orange

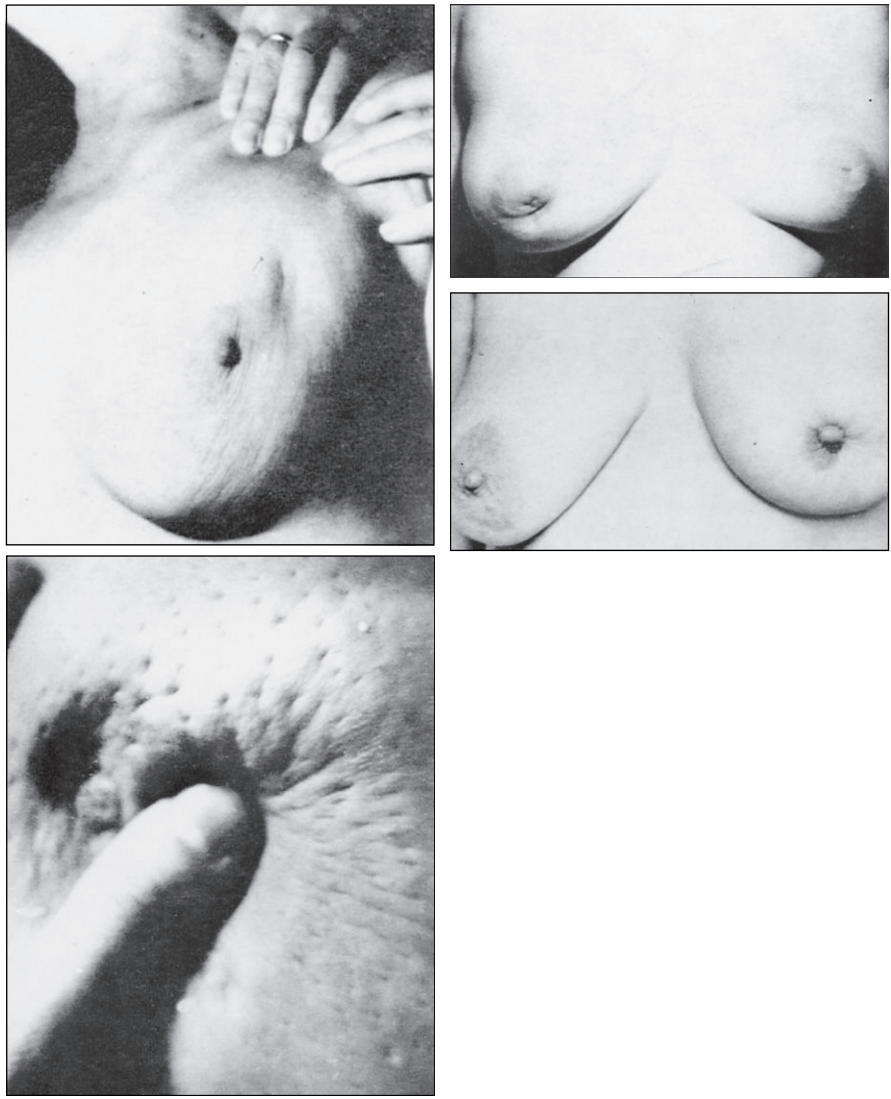

FIGURE 4.14 Peau d'orange

Reproduced, with permission, from Katz JW, Falace DA, Miller CS, Rhodus NL, *Comprehensive Gynecology*, 5th edn, Philadelphia: Mosby, 2007: Fig 15-13B.

DESCRIPTION

Literally meaning 'skin of an orange', it is a term used to describe a dimpled appearance of the breast skin.

CONDITION/S ASSOCIATED WITH

More common

- Breast cancer
- Breast abscess

Less common

- Myxoedema

GENERAL MECHANISM/S

Inflammation and/or oedema that accentuates the depressions at the base of the hair follicles.

Breast cancer

Cancer tissue causes the destruction and or/blockage of the lymphatics. Skin drainage is compromised and lymphoedema develops, along with thickening and swelling of the skin. Accentuation of the depressions of the skin at the site of the hair follicles produces the dimples.

Tethering of the thickened skin to the underlying *Cooper's ligaments* creates the orange peel appearance.[45]

SIGN VALUE

Although there are few studies on the prevalence of peau d'orange in breast cancer, if found on exam further investigation is mandatory.

Prostate (abnormal)

DESCRIPTION

On digital rectal examination the prostate can be both felt and assessed and is normally described as rubbery and walnut-sized on palpation. Abnormalities the examiner may find are:

1. hard, irregular and/or enlarged nodular prostate
2. boggy tenderness – prostatitis.

CONDITION/S ASSOCIATED WITH

- Prostate cancer
- Benign prostatic hypertrophy (BPH)
- Prostatitis

PROSTATE CANCER MECHANISM/S

The tumour or benign mass expands the prostate in an irregular fashion and thus, in theory, creates irregular nodules and alterations in size and shape. Most prostate cancers originate in the peripheral zones of the prostate and thus, in theory, should be easier to palpate. The underlying cause of prostate cancer is still being determined.

PROSTATITIS MECHANISM/S

Anything that may cause inflammation of the gland may present with a painful, boggy prostate gland.

The most frequent causes of inflammation of the prostate are bacterial infections, which can be caused idiopathically or via sexual intercourse or arise from recurrent urinary tract infections of the prostate gland. Infection leads to inflammation, oedema (boggyness) and stimulation of pain fibres, causing tenderness.

PROSTATE CANCER SCREENING

At the time of publication, prostate cancer screening (in conjunction with prostate-specific antigen [PSA]) is under intense review. However, there is some evidence of the value of an expertly performed digital rectal exam (DRE):

- Prior to PSA screening, DRE is said to identify 40–50% of biopsy-detected cancers.[46]
- With PSA screening, the number of patients detected on DRE alone has declined – the predictive accuracy of PSA does outperform that of DRE.[47]
- However, potentially aggressive cancers are more prevalent in men who have an abnormal DRE.[47,48]
- A substantial proportion of patients with aggressive cancers were found on DRE alone.[49]

Given the low cost of DRE, despite the discomfort to the patient (and often the examiner), there is still value to the idea that 'if you don't put your finger in it, you put your foot in it.'

Rectal mass

DESCRIPTION

Palpation of an irregular/unexpected mass in the rectum on digital rectal examination (DRE).

CONDITION/S ASSOCIATED WITH

- Rectal cancer

COLORECTAL CANCER SCREENING

There are limited studies regarding the true value of DRE findings in surveillance for colorectal cancer. The available evidence for detection of palpable tumour is underwhelming.

- One meta-analysis[50] showed sensitivity of 64%, specificity of 97% and PPV of 0.47.
- Another more recent study[51] showed sensitivity of 76.2%, specificity of 93% and a low of PPV of 0.3.

Based on the above results, it is suggested that, in the primary care setting, DRE is an inaccurate and poor predictor of colorectal cancer and that there is a high risk of false positive findings, resulting in inappropriate further referral for investigation. However, many tumours are still first noticed during DRE.

Trousseau's sign of malignancy

DESCRIPTION

Initially described by Trousseau as the observation of a *migratory thrombophlebitis preceding diagnosis of occult malignancy*. Over time it has been used to describe virtually any thrombotic event associated with malignancy.

In today's setting, it is most easily thought of as any unexplained thrombotic event that precedes identification of occult visceral malignancy.[52]

N.B. Not to be confused with Trousseau's sign in hypocalcaemia – see Chapter 7, 'Endocrinology signs'.

CONDITION/S ASSOCIATED WITH

More common

- Lung cancer

Less common

- Pancreatic cancer
- Gastric cancer
- Colon cancer
- Prostate cancer

MECHANISM/S

The exact mechanism of thrombotic events due to occult malignancy is multifaceted and, as such, not fully understood or proven. However, all of the pathways ultimately result in the activation of the coagulation system.

Contributing factors/theories are discussed under the following headings.

Tissue factor

Evidence has shown that some carcinomas:

- expose endothelium-based tissue factor (TF).
- via expression of tumour oncogenes and inactivation of tumour suppressor genes, lead to increased TF levels
- may actually produce TF in microvesicles.

All of these can, in turn, activate the clotting cascade and platelet aggregation at sites distant from the local tumour.[53]

Carcinoma mucins

Mucins are large, heavily glycosylated molecules. Some tumours produce large amounts of mucins, which then interact with P and L selectins to activate tissue multiple pathways to produce platelet plugs and microthrombi and, hence, thrombophlebitis.

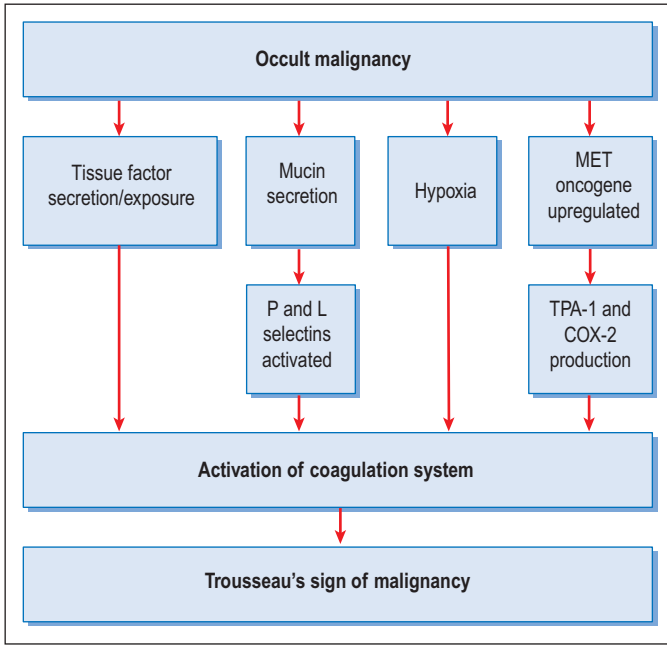

FIGURE 4.15 Mechanism of Trousseau's sign of malignancy

Oncogene activation

More recently, activation of the MET oncogene has been postulated to activate tissue plasminogen activator 1 and cyclooxygenase 2, which in turn influence coagulation and haemorrhagic pathways.[54]

Tissue hypoxia

Tissue hypoxia causing increased expression of genes that facilitate coagulation (e.g. plasminogen activator inhibitor-1 [PAI-1]) has also been proposed as a contributing factor.[55] Definitive research on this is lacking.

SIGN VALUE

Direct studies on the sensitivity and specificity of Trousseau's sign are minimal. 11% of all cancer patients will develop thrombophlebitis,[56] whereas 23% of patients may have evidence of it at autopsy.[57] Whereas robust evidence for its use as a valuable sign in malignancy is lacking, in patients who develop multiple thrombotic events without identifiable cause, cancer must always be considered.

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CHAPTER 5

Neurological Signs

Understanding the mechanisms and clinical significance of neurological signs poses several challenges that are unique to the neurological system:

- the relevance of neuroanatomy and topographical anatomy
- patterns of multiple clinical signs
- examination methods with significant inter-examiner variabilities.

Throughout the chapter, we have tried to present neuroanatomical and pathophysiological concepts in a succinct and clinically relevant manner, without forfeiting critical information.

Guide to the 'Relevant neuroanatomy and topographical anatomy' boxes

The explanations of signs in this chapter include additional sections in boxes titled 'Relevant neuroanatomy and topographical anatomy'. Understanding these two aspects of neural pathways is critical to understanding the mechanisms of neurological signs.

For example, the most common mechanism of bitemporal hemianopia is compression of the optic chiasm by an enlarging pituitary macroadenoma. The pituitary gland is located directly inferior to the optic chiasm (i.e., the relevant topographical anatomy). The nerve fibres of the optic chiasm supply each medial hemiretina, and thus transmit visual information from each temporal visual hemifield (i.e., the relevant neuroanatomy). Dysfunction of these nerve fibres results in bitemporal hemianopia.

Symbols have been used to signify important components of the relevant anatomical pathways.

KEY TO THE SYMBOLS USED IN THE 'RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY' BOXES

- • Relevant primary neuroanatomical structures in the pathway(s)
- ⇒ Significant topographical anatomical structure(s)
- → Associated neuroanatomical pathway(s)
- ∅ Decussation (i.e., where the structure crosses the midline)
- × An effector (e.g. muscle)
- ⊗ A sensory receptor
- ↔ Structure receives bilateral innervation

Abducens nerve (CNVI) palsy

DESCRIPTION

There is impaired abduction and mild esotropia (i.e., medial axis deviation) of the abnormal eye.[1] Dysconjugate gaze worsens when the patient looks towards the side of the lesion (see Figure 5.1B).

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[1,2]

- Abducens nuclei, dorsal pons
- → Facial nerve fascicles
- ↓
- Abducens fascicles
- ↓
- Abducens nerve
- → Medial longitudinal fasciculus (MLF)
- ⇒ Subarachnoid space
- ⇒ Clivus
- ⇒ Petroclinoid ligament in Dorello's canal
- ⇒ Cavernous sinus
- ⇒ Cavernous segment, internal carotid artery
- ⇒ Superior orbital fissure
- ⇒ Orbital apex
- ↓
- × Lateral rectus muscle

CONDITION/S ASSOCIATED WITH[1–3]

Common

- Blunt head trauma
- Diabetic mononeuropathy/ microvascular infarction

Less common

- 'False localising sign' in elevated intracranial pressure
- Cavernous sinus syndrome
- Cavernous carotid artery aneurysm
- Giant cell arteritis
- Cerebellopontine angle tumour

MECHANISM/S

Abducens nerve dysfunction causes ipsilateral lateral rectus muscle weakness (see Table 5.1 for mechanisms of clinical features in abducens nerve palsy). Abducens nerve palsy is caused by peripheral lesions of the abducens nerve (CNVI). Lesions of the abducens nuclei result in horizontal gaze paresis (i.e., ipsilateral abduction paresis and contralateral adduction weakness) due to an impaired coordination of conjugate eye movements with the oculomotor motor nuclei, via the medial longitudinal fasciculus (MLF).

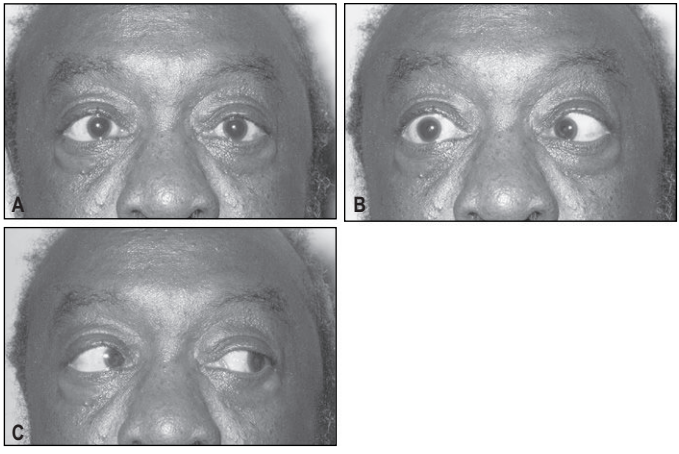

FIGURE 5.1 Right abducens nerve (CNVI) palsy

A, primary gaze position with mild esotropia (right eye deviates nasally); **B**, right gaze with impaired abduction; **C**, normal left gaze.

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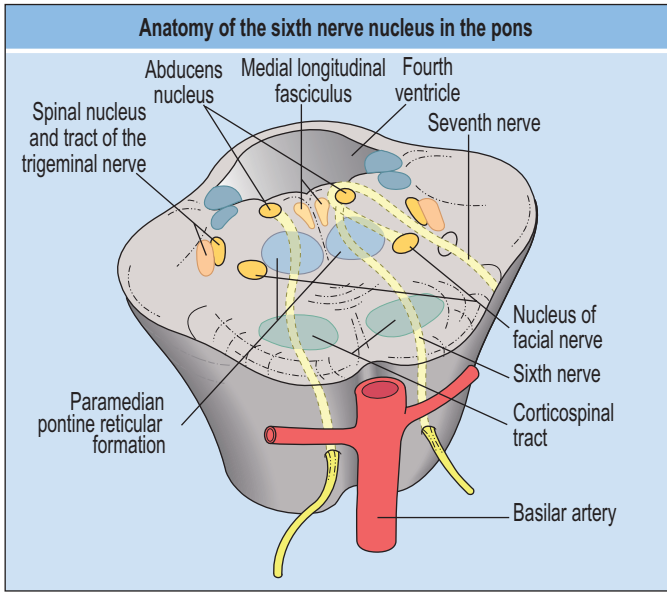

FIGURE 5.2 Anatomy of the abducens nuclei and facial nerve fascicles

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TABLE 5.1 Mechanisms of clinical features in abducens nerve palsy

Clinical features	Mechanism
• Impaired abduction	→ Lateral rectus muscle weakness
• Esotropia	→ Unopposed medial rectus muscle

Causes of abducens nerve (CNVI) palsy include:

1. disorders of the subarachnoid space
2. diabetic mononeuropathy and microvascular infarction
3. elevated intracranial pressure, the 'false localising sign'
4. cavernous sinus syndrome
5. orbital apex syndrome.

Disorders of the subarachnoid space

Mass lesions (e.g. aneurysm, tumour, abscess) may compress the abducens nerve as it traverses the subarachnoid space. The abducens nerve emerges from the brainstem adjacent to the basilar and vertebral arteries, and the clivus. Aneurysmal dilation of these vessels and/or infectious or inflammatory conditions of the clivus can compress the abducens nerve.[1] Often, multiple cranial nerve abnormalities (e.g., CNVI, VII, VIII) coexist since these structures lie in close proximity to one another upon exiting the brainstem.[1]

Diabetic mononeuropathy and microvascular infarction

Diabetic vasculopathy of the vasa nervorum (i.e., disease of the the blood supply of the nerve) may result in microvascular infarction of the abducens nerve.[3]

Elevated intracranial pressure, the 'false localising sign'

Due to the relatively fixed nature of the abducens nerve at the pontomedullary sulcus and at the point of entry into Dorello's canal, it is vulnerable to stretch and/or compression injury secondary to elevated intracranial pressure.[1,2] In this setting, abducens nerve (CNVI) palsy is sometimes labelled a 'false localising sign' due to the misleading localising nature of the finding. Causes of elevated intracranial pressure include mass lesions (e.g. tumour, abscess), cerebral haemorrhage, idiopathic intracranial hypertension (IIH), central venous sinus thrombosis and hydrocephalus.

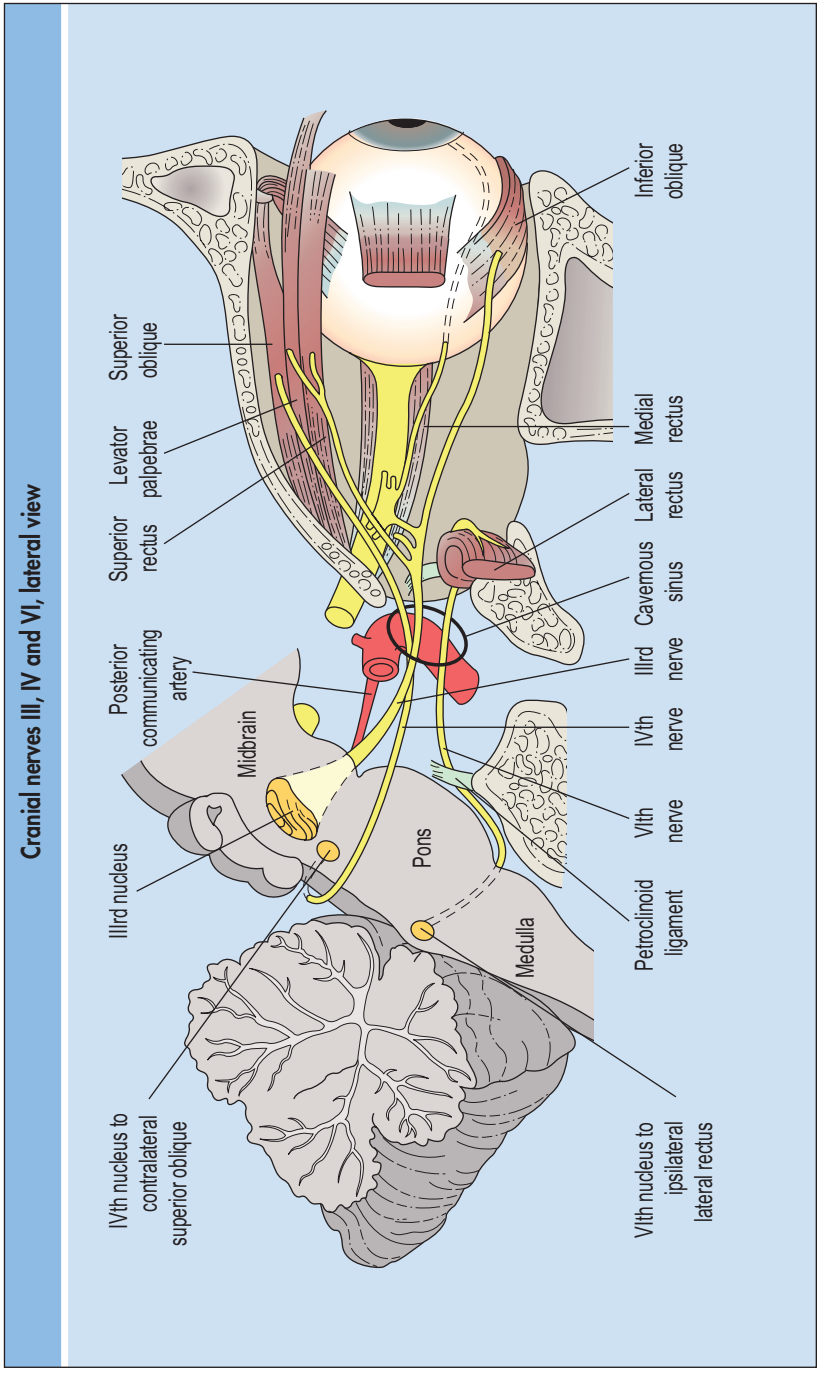

FIGURE 5.3 Lateral view of the abducens nerve (CNVI) and extraocular structures

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Cavernous carotid artery aneurysm and cavernous sinus syndrome

The cavernous segment of the abducens nerve is located adajcent to the cavernous carotid artery, and is prone to compression by aneurysmal dilation of the vessel.
See 'Cavernous sinus syndrome' in this chapter.

Orbital apex syndrome

See 'Orbital apex syndrome' in this chapter.

SIGN VALUE

Abducens nerve palsy is caused by a variety of peripheral nerve lesions and is the most common 'false localising sign' in elevated intracranial pressure.

Anisocoria

DESCRIPTION

Anisocoria is a difference between pupil diameters of at least 0.4 mm.[4]

Anisocoria in normal individuals without neurological disease is termed physiological anisocoria. Physiological anisocoria occurs in 38% of the population. The difference in pupil diameter is rarely greater than 1.0 mm.[5]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[6,7]

Pupillary constriction/parasympathetic pathway

EFFERENT LIMB

- Edinger–Westphal nucleus midbrain

↓

- Oculomotor nerve (CNIII)
- ⇒ Posterior communicating artery (PComm), circle of Willis
- ⇒ Uncus, medial temporal lobe
- ⇒ Superior orbital fissure, sphenoid bone
- ⇒ Cavernous sinus
- ⇒ Orbital apex

↓

- Ciliary ganglion

↓

- Short ciliary nerves

↓

- × Pupillary constrictor muscles
- × Levator palpebrae muscle
- × Iris

Pupillary dilation/sympathetic pathway

FIRST-ORDER NEURON

- Hypothalamus

↓

- Sympathetic fibres, brainstem

↓

- Sympathetic fibres, intermediate horn, spinal cord
- ⇒ Central canal spinal cord

↓

SECOND-ORDER NEURON (PREGANGLIONIC FIBRE)

- Sympathetic trunk
- ⇒ Lung apex

↓

- Superior cervical ganglion (C2)

↓

THIRD-ORDER NEURON (POSTGANGLIONIC FIBRE)

- Superior cervical ganglion (C2)
- ⇒ Carotid sheath
- ⇒ Carotid artery
- ⇒ Superior orbital fissure
- ⇒ Cavernous sinus
- ⇒ Orbital apex

↓

- Ciliary body

↓

- × Pupillary radial muscles
- × Superior tarsal muscle
- × Sweat glands

Eye structures

- ⇒ Cornea
- ⇒ Anterior chamber
- ⇒ Iris
- × Pupillary constrictor muscles
- × Pupillary radial muscles

CONDITION/S ASSOCIATED WITH[4,7,8]

Common

- Physiological anisocoria
- Drugs (e.g., atropine, salbutamol, ipratropium, cocaine)
- Horner's syndrome

Less common

- Oculomotor nerve (CNIII) palsy
- Acute angle closure glaucoma
- Anterior uveitis
- Adie's tonic pupil

MECHANISM/S

Physiological anisocoria may result from asymmetrical inhibition of the Edinger–Westphal nuclei in the midbrain.[9]

Pathological anisocoria is caused by:

- pupil constrictor muscle weakness – mydriasis
- pupil dilator muscle weakness – miosis
- pupil constrictor muscle spasm – miosis.

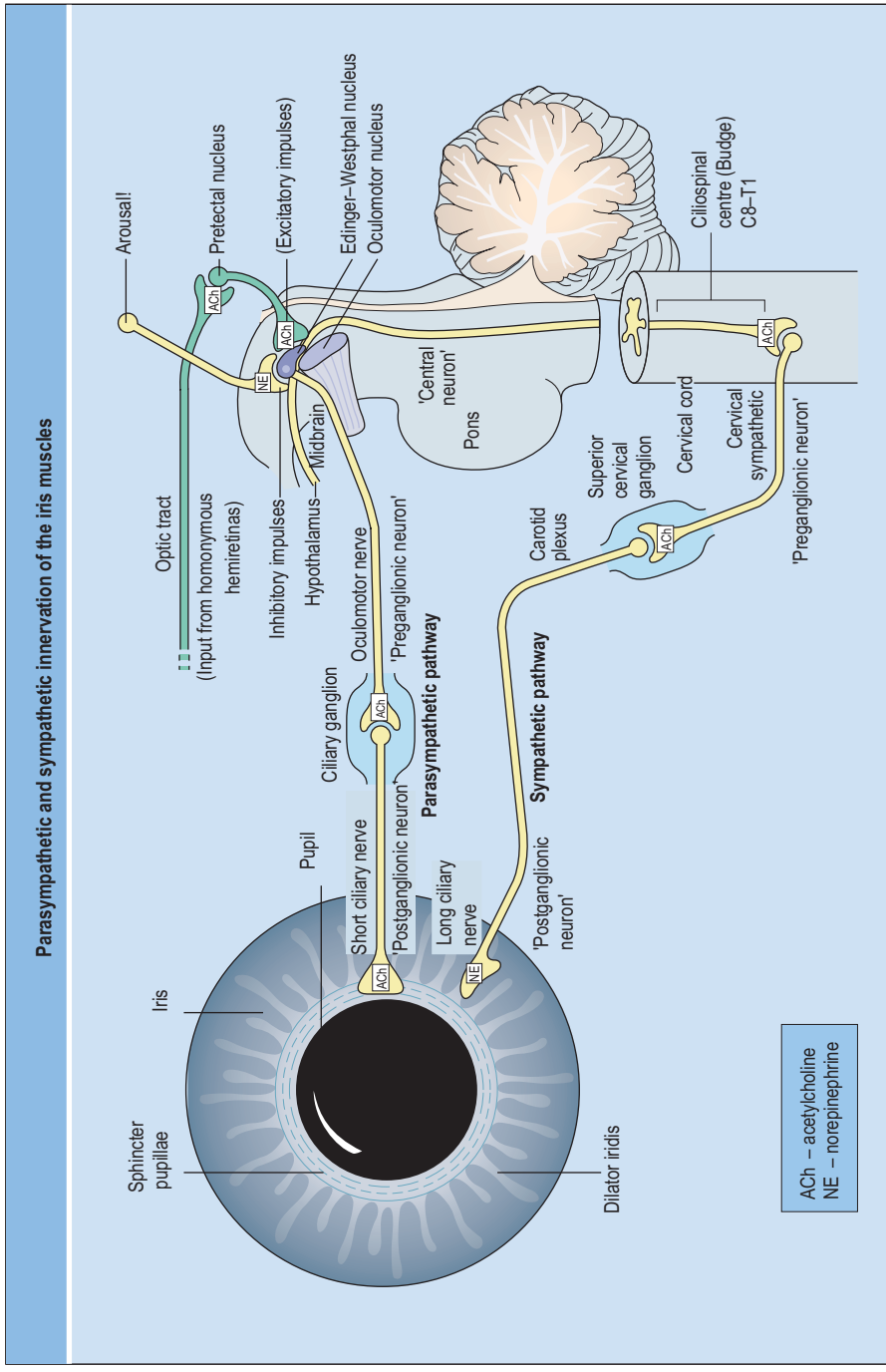


FIGURE 5.4 Parasympathetic and sympathetic innervation of the pupillary muscles

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn. St Louis: Mosby, 2008: Fig 9-19-5.

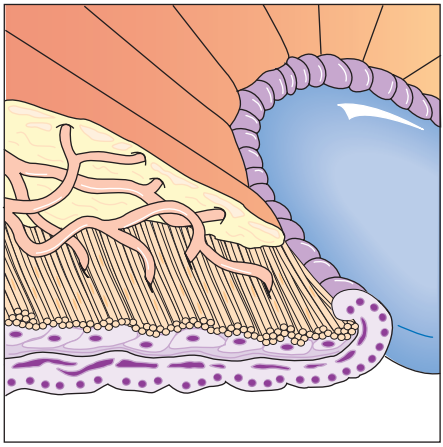


FIGURE 5.5 Circumferential distribution of the pupillary constrictor muscles and radial distribution of the pupillary dilator muscles

Based on Dyck PJ, Thomas PK, *Peripheral Neuropathy*, 4th edn. Philadelphia: Saunders, 2005: Fig 9-1.

Disorders of the afferent limb of the pupillary light reflex do not cause anisocoria because the optic nerves (CNII) form bilateral and symmetric connections with each oculomotor nucleus, such that pupillary responses to changes in ambient light are equal.[4]

At first glance, it may not be obvious which eye is the abnormal eye. The abnormal eye typically has a decreased or absent pupillary light response. To identify the abnormal eye, the degree of anisocoria is reassessed in low light (i.e., in the dark) and reassessed in bright light.[8] If the magnitude of anisocoria increases in the dark (i.e., the normal pupil dilates appropriately), then the abnormal eye has the smaller pupil. If the magnitude of anisocoria increases in bright light (i.e., the normal pupil constricts appropriately), the abnormal eye has the larger pupil.

Mechanism – anisocoria more prominent in the dark

Anisocoria that worsens in the dark is caused by an abnormally small pupil (i.e., miosis). For bilateral small pupils, see 'Pinpoint pupils' and 'Argyll Robertson pupils' in this chapter. Causes of an abnormally small pupil include:[6]

1. Horner's syndrome
2. pupillary constrictor muscle spasm
3. drugs.

HORNER'S SYNDROME[10–12]

Horner's syndrome is caused by a lesion of the sympathetic pathway at one of three levels: 1) first-order neuron, 2) second-order neuron or 3) third-order neuron. Horner's syndrome is a triad of miosis, ptosis with apparent enophthalmos and anhydrosis (see 'Horner's syndrome' in this chapter).

PUPILLARY CONSTRICTOR MUSCLE SPASM

Inflammation of the iris and/or anterior chamber may irritate the pupillary constrictor muscle resulting in spasm and miosis. Associated features may include visual acuity loss, photophobia, a red eye and a pupil with an irregular margin. Causes of pupillary constrictor muscle spasm include traumatic iritis and anterior uveitis.

DRUGS

Systemic drug toxicity generally causes symmetrical changes in the pupils. Drug-induced anisocoria is more likely to be caused by unilateral topical drug exposure (may be unintentional or iatrogenic). Muscarinic agonists (e.g. pilocarpine), adrenergic antagonists (e.g. timolol) and opioids (e.g. morphine) cause pupil constriction (see 'Pinpoint pupils' in this chapter).

Mechanism – anisocoria more prominent in bright light

Anisocoria that increases in bright light is caused by an abnormally large pupil (i.e., mydriasis). Causes of an abnormally large pupil include:[6]

1. oculomotor nerve (CNIII) palsy
2. Adie's tonic pupil
3. damage to the neuromuscular structures of the iris
4. drugs.

OCULOMOTOR NERVE (CNIII) PALSY

The oculomotor nerve innervates the pupillary constrictor muscle, levator palpebrae muscle and all extraocular muscles, except the superior oblique and lateral rectus muscles. Oculomotor nerve palsy results in ipsilateral mydriasis due to weakness of the pupillary constrictor muscle. Oculomotor nerve palsy may be 'complete' (i.e., gaze palsy, ptosis and

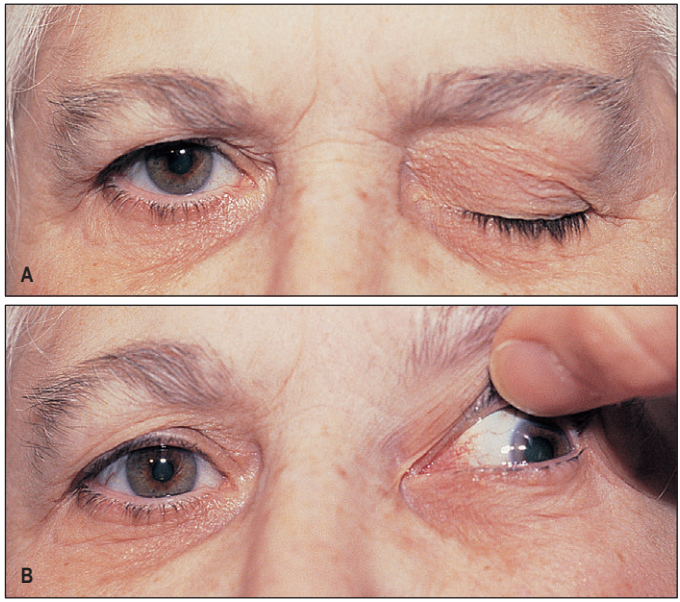


FIGURE 5.6 Complete left oculomotor nerve palsy: **A** complete ptosis; **B** left exotropia and left hypotropia

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 11-10-2.

mydriasis), 'pupil sparing' (i.e., gaze palsy and ptosis) or limited to the pupil (i.e., mydriasis only). Causes include posterior communicating (PComm) artery aneurysm, diabetic mononeuropathy/microvascular infarction, uncal herniation, ophthalmoplegic migraine, cavernous sinus syndrome and orbital apex syndrome[7,13] (see 'Oculomotor nerve (CNIII) palsy' in this chapter).

ADIE'S TONIC PUPIL

The four characteristics of Adie's tonic pupil are:[4,14–16]

1. unilateral mydriasis
2. decreased or absent pupillary light response
3. light–near dissociation
4. pupillary constrictor muscle sensitivity to pilocarpine.

Adie's tonic pupil is caused by injury to the ciliary ganglion and/or postganglionic fibres and results in abnormal regrowth of the short ciliary nerves.[4] Normally, the ciliary ganglion sends 30 times more nerve fibres to the ciliary muscle than the pupillary constrictor muscle. Aberrant regrowth of the ciliary nerves (a random process) favours reinnervation of the pupillary sphincter, rather than the ciliary muscle, in a 30:1 ratio.[14–16] Causes of Adie's tonic pupil include orbital trauma, orbital tumours and varicella zoster infection in the ophthalmic division of the trigeminal nerve (CNV V1).

DAMAGE TO THE NEUROMUSCULAR STRUCTURES OF THE IRIS

Traumatic injury, inflammation or ischaemia of the neuromuscular structures of the iris may result in a slow, mid-range or dilated pupil.[9] Associated features include an irregular pupil margin, photophobia, decreased visual acuity and decreased pupillary light response. Causes include ocular trauma (e.g. globe rupture), endophthalmitis and acute angle closure glaucoma.

DRUGS

Systemic drug toxicity typically results in symmetrical changes in pupil diameter. Anisocoria is more likely to be caused by unilateral topical exposure (may be unintentional or iatrogenic). For example, unilateral ocular exposure can occur during the administration of nebulised salbutamol in a patient with a loosely fitting mask. Causes include cholinergic antagonists (e.g. atropine, ipratropium) and adrenergic agonists (e.g. cocaine, salbutamol).[9]

SIGN VALUE

Anisocoria may be a sign of a potentially life-threatening condition (e.g. an enlarging posterior communicating (PComm) artery aneurysm associated with subarachnoid haemorrhage) or an acute eye-threatening condition (e.g. acute angle closure glaucoma). The first step is to identify the abnormal eye.

Anosmia

DESCRIPTION

Anosmia is absence of the sense of smell. Hyposmia is a decreased ability to recognise smells. Disorders of olfaction may be unilateral or bilateral.[17] Olfaction is assessed with familiar scents such as coffee or mint. Noxious substances stimulate sensory fibres of the trigeminal nerve and may confound the evaluation.[17] Sensory nerve endings of the trigeminal nerve respond nonselectively to volatile substances, giving the sensation of general nasal irritability.[17]

NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[6,18]

- Olfactory neuroepithelium
- ↓
- Olfactory nerves
- ⇒ Cribriform plate, ethmoid bone
- ↓
- Olfactory bulb
- ⇒ Olfactory sulcus, inferior frontal lobe
- ↓
- Olfactory tracts
- ↓
- Olfactory cortex, medial temporal lobe
- ↓
- Thalamus, entorhinal cortex, hippocampus, amygdala

CONDITION/S ASSOCIATED WITH[17,19,20]

Common

- Upper respiratory tract infection (URTI)
- Chronic allergic or vasomotor rhinitis
- Trauma
- Cigarette smoking
- Normal ageing
- Alzheimer's disease

Less common

- Tumour (e.g. meningioma)
- Iatrogenic
- Meningitis
- Drugs
- Kallman's syndrome

MECHANISM/S

Aetiologies of anosmia are either intranasal or neurogenic in origin.[17] Causes of anosmia include:[17,19,20]

1. olfactory cleft obstruction
2. inflammatory disorders of the olfactory neuroepithelium
3. traumatic injury of the olfactory nerves
4. olfactory bulb or tract lesion
5. degenerative disease of the cerebral cortex
6. normal ageing.

Olfactory cleft obstruction

Mechanical airway obstruction impairs the transmission of odoriferous substances to the olfactory receptor cells on the olfactory neuroepithelium. Causes include nasal

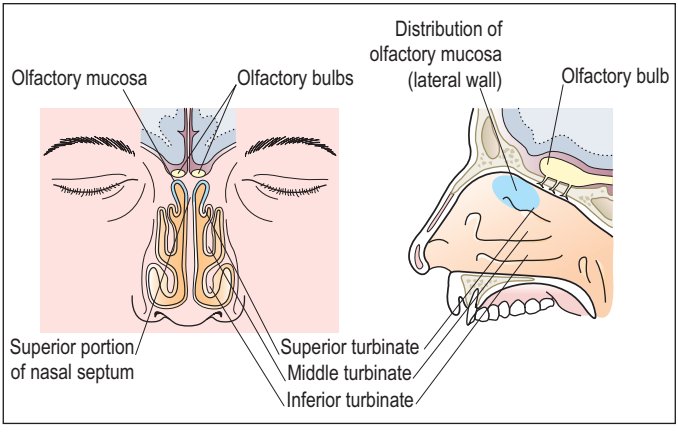


FIGURE 5.7 Functional anatomy of the peripheral olfaction pathway

Reproduced, with permission, from Bromley SM, Am Fam Physician 2000; 61(2): 427–436: Fig 2A.

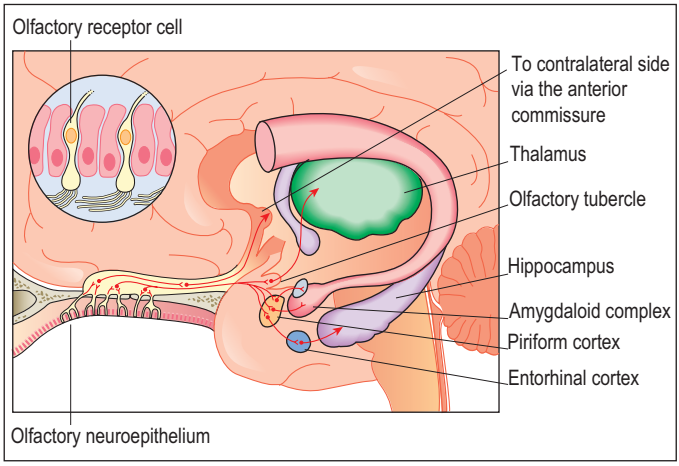


FIGURE 5.8 Functional anatomy of the central olfaction pathway

Reproduced, with permission, from Bromley SM, Am Fam Physician 2000; 61(2): 427–436: Fig 2B.

polyposis, tumour, foreign body and excess secretions.[21]

Inflammatory disorders of the olfactory neuroepithelium

Inflammation of the olfactory mucosa can cause dysfunction of the olfactory neuroepithelium.[21] Alterations in nasal air flow, mucociliary clearance, secretory product obstruction, polyps or retention cysts likely contribute to olfactory neuroepithelium dysfunction.[22] Causes include URTI, allergic or vasomotor rhinitis and cigarette smoking.

Traumatic injury of the olfactory nerves

Stretching and shearing of the olfactory nerves may occur in rapid acceleration–deceleration type injuries (e.g. motor vehicle collision) as the olfactory nerves are fixed in the cribriform plate of the ethmoid bone. Direct penetrating or blunt injury to the structures of the olfactory system is also possible.[23]

Olfactory bulb or tract lesion

Intracranial masses at the base of the frontal lobes can cause dysfunction of the olfactory bulbs and/or olfactory tracts due to mass effect. Causes include meningioma, metastases, complicated meningitis and sarcoidosis.[6,17] Diseases of the ethmoid bone may result in compression of the olfactory neurons as they traverse the cribriform plate. Causes include Paget's disease, osteitis fibrosa cystica, bony metastases and trauma.

Neurodegenerative disease of the cerebral cortex

In Alzheimer's disease, there is degeneration of the medial temporal lobe and other cortical areas involved in olfactory processing.[24] Other neurodegenerative cortical diseases associated with anosmia include Lewy body dementia, Parkinson's disease and Huntington's chorea.[17]

Normal ageing

Age-related olfactory changes include reduced olfactory sensitivity, intensity, identification and discrimination. These changes may be due to dysfunction at the receptor or neuron level secondary to underlying disease states, pharmacological agents or changes in hormonal and neurotransmitter levels.[17]

SIGN VALUE

Anosmia is an important sign associated with a frontal lobe lesion (e.g. meningioma) and neurodegenerative disorders (e.g. Alzheimer's disease), but is most commonly caused by intranasal disorders. In a study of 278 consecutive patients with anosmia or hyposmia evaluated in an ENT clinic, the aetiology was upper respiratory tract infection in 39%, sinonasal disease in 21%, idiopathic in 18%, trauma in 17% and congenital in 3% of patients.[25]

Argyll Robertson pupils and light–near dissociation

DESCRIPTION

Arygll Robertson pupils are characterised by:[4,9]

1. small pupils
2. absence of the pupillary light response
3. brisk accommodation reaction
4. bilateral involvement.

Light–near dissociation is defined as:[4,9]

1. a normal accommodation response
2. a sluggish or absent pupillary light response.

Light–near dissociation is said to be present if the near pupillary response (tested in moderate light) exceeds the best pupillary response with a bright light source.[9] Light–near dissociation is associated with Argyll Robertson pupils (classically, a sign of tertiary syphilis).

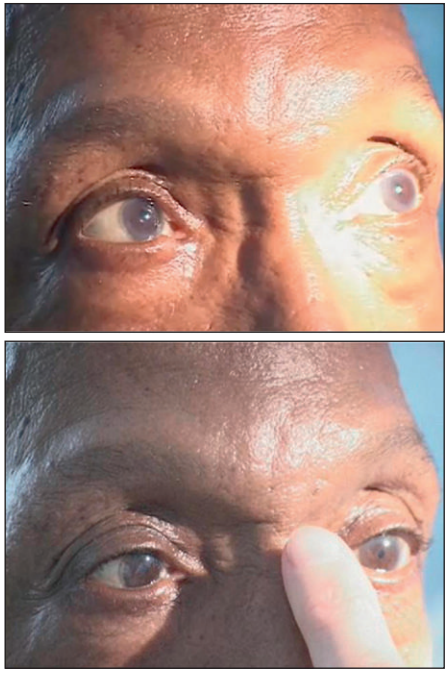


FIGURE 5.9 Argyll Robertson physical findings

Top, lack of pupillary constriction to light; bottom, pupillary constriction to accommodation.

Reproduced, with permission, from Aziz TA, Holman RP, Am J Med 2010; 123(2): 120–121.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[6]

Accommodation and pupillary light pathways

AFFERENT STRUCTURES

- Retinal neuroepithelium
- ↓
- Optic nerve (CNII)
- ↓
- Pretectal nucleus midbrain
- ↓
- ↔ Bilateral innervation of Edinger–Westphal nuclei
- ↓

EFFERENT STRUCTURES

- Visual cortex (accommodation only)
- ↓
- Accommodation area, visual cortex (accommodation only)
- ↓
- Pretectal nuclei, midbrain
- ↓
- Edinger–Westphal nuclei, midbrain
- ↓
- Oculomotor nerve (CNIII)
- ↓
- Ciliary ganglion
- ↓
- Short ciliary nerves
- ↓
- × Pupillary constrictor muscles
- × Ciliary muscle
- × Medial rectus muscles

CONDITION/S ASSOCIATED WITH[6,9,26,27]

- Multiple sclerosis
- Neurosarcoidosis
- Tertiary syphilis

MECHANISM/S

Argyll Roberston pupils and light–near dissociation are caused by a pretectal lesion in the dorsal midbrain affecting

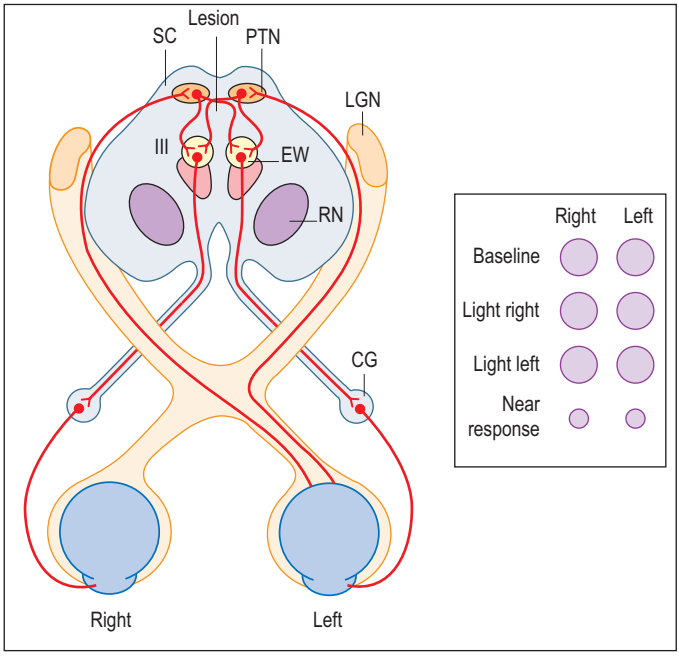


FIGURE 5.10 Pupillary response associated with light–near dissociation due to lesion in the pretectum

CG = ciliary ganglion; EW = Edinger–Westphal nucleus; LGN = lateral geniculate nucleus; PTN = pretectal nucleus; RN = red nucleus; SC = superior colliculus.

Reproduced, with permission, from Goldman L, Ausiello D, *Cecil Medicine*, 23rd edn, Philadelphia: Saunders, 2007: Fig 450-2.

the fibres of light reflex, which spare the fibres of the accommodation pathway that innervate the Edinger–Westphal nuclei[26] (see Figure 5.10).

SIGN VALUE

Argyll Robertson pupils are classically a sign of tertiary syphilis. Tertiary syphilis is no longer the most common cause of light–near dissociation.

Ataxic gait

DESCRIPTION

An ataxic gait has a 'drunken' or staggering quality and is characterised by a wide-based stance to accommodate truncal instability.[28] It becomes more pronounced on a narrow base, during heel-to-toe walking and during rapid postural adjustments.[28]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[6]

CEREBELLUM

- Vermis and flocculonodular lobe
  - → Anterior corticospinal tract
  - → Reticulospinal tract
  - → Vestibulospinal tract
  - → Tectospinal tract
- Paravermal (intermediate) hemisphere
  - → Lateral corticospinal tract
  - → Rubrospinal tract
  - Lateral hemisphere
  - → Lateral corticospinal tract

CONDITION/S ASSOCIATED WITH[6,28,29]

Common

- Alcohol misuse
- Cerebellar infarction
- Cerebellar haemorrhage
- Hereditary cerebellar degeneration (e.g. Freidreich's ataxia)
- Multiple sclerosis
- Drugs (e.g. benzodiazepines, lithium, phenytoin)

Less common

- Vertebral artery dissection
- Mass lesion (e.g. tumour, abscess)
- HSV cerebellitis
- Paraneoplastic cerebellar degeneration

MECHANISM/S

Ataxic gait is typically a midline cerebellar sign. It may also be associated with hemispheric cerebellar lesions. Dysfunction of the midline cerebellar structures (e.g. vermis, flocculonodular lobes, intermediate lobe) results in impaired trunk coordination, dysequilibrium and increased body sway (i.e., truncal ataxia).[28] Causes of ataxic gait include:

1. cerebellar vermis lesion
2. flocculonodular lobe lesion
3. intermediate hemisphere lesion
4. lateral hemisphere lesion.

Cerebellar vermis lesion

Isolated lesions of the cerebellar vermis may cause pure truncal ataxia with paucity of hemispheric cerebellar signs (e.g. dysmetria, dysdiadochokinesis, intention tremor).[28] Lower limb coordination during

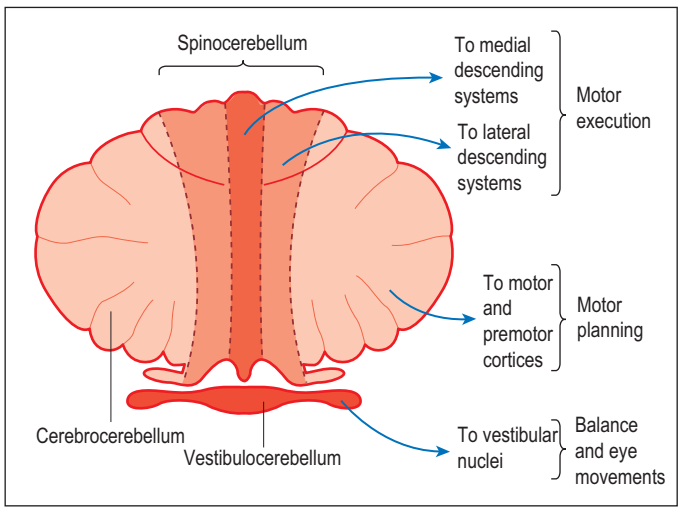


FIGURE 5.11 Functional anatomy of the cerebellum (see also Table 5.2)

Reproduced, with permission, from Barrett KE, Barman SM, Boitano S et al. *Ganong's Review of Medical Physiology*, 23rd edn. Available: http://accessmedicine.com [9 Dec 2010].

TABLE 5.2 Functional anatomy of the cerebellum and associated motor pathways

Cerebellar anatomy	Function	Associated motor pathways
Vermis and flocculonodular lobe	• Proximal limb and trunk coordination • Vestibulo-ocular reflexes	• Anterior corticospinal tract • Reticulospinal tract • Vestibulospinal tract • Tectospinal tract
Intermediate hemisphere	• Distal limb coordination	• Lateral corticospinal tracts • Rubrospinal tracts
Lateral hemisphere	• Motor planning, distal extremities	• Lateral corticospinal tracts

Adapted from Blumenfeld H, *Neuroanatomy Through Clinical Cases*, Sunderland: Sinauer, 2002.

the heel-to-shin test may be relatively normal during supine examination.[28]

Flocculonodular lobe lesion

Lesions of the flocculonodular lobe are characterised by multidirectional truncal instability, dysequilibrium and severe impairment of trunk coordination.[28] Patients may be unable to stand or sit although, when in the supine position, the heel-to-shin test may be normal.[28]

Intermediate hemisphere lesion

Low-frequency forwards and backwards truncal sway and a rhythmic trunk and head tremor may be present with the ataxic gait.[28]

Lateral hemisphere lesion

Hemispheric lesions usually cause ipsilateral abnormalities in coordinated leg movements, and stepping is irregular in timing, length and direction.[28] Stepping is typically slow and careful, and instability is accentuated during heel-to-toe walking.[28] Associated features include dysmetria, dysdiadochokinesis and intention tremor.

SIGN VALUE

Ataxic gait is typically a midline cerebellar sign, but may be present in hemispheric cerebellar lesions. In multiple studies of 444 patients with unilateral cerebellar lesions, ataxic gait was present in 80–93% of patients.[4,30]

Atrophy (muscle wasting)

DESCRIPTION

There is decreased muscle tissue bulk. Moderate-to-severe unilateral muscle wasting is typically apparent on gross inspection with the unaffected side. Comparison of axial limb circumference is a reliable method for identifying subtle asymmetrical muscle wasting.[4,18]

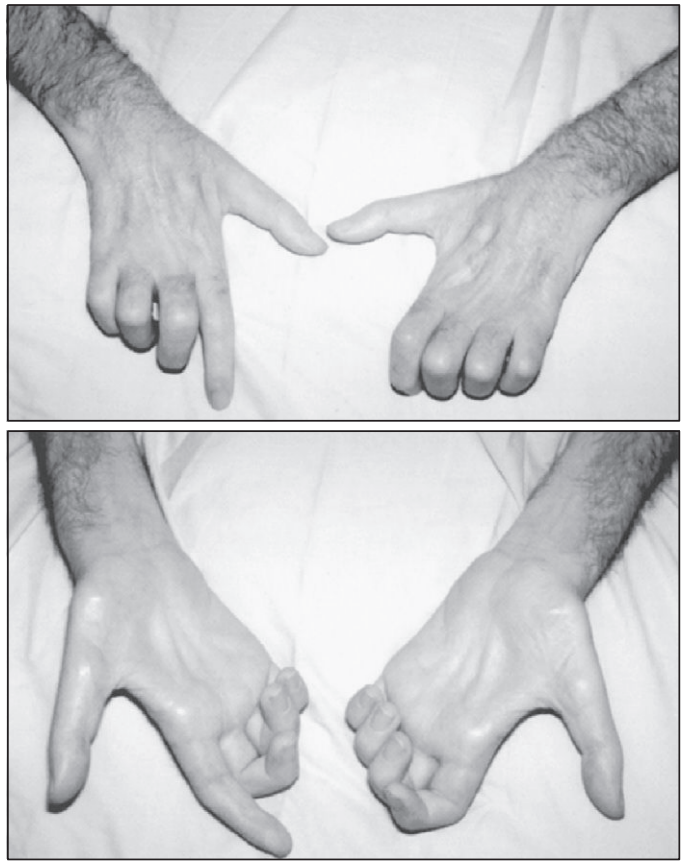


Figure 5.12 Muscle wasting in the intrinsic hand muscles in a patient with amyotrophic lateral sclerosis

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 78-4.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

UPPER MOTOR NEURON
- Upper motor neuron

LOWER MOTOR NEURON
- Anterior horn grey matter, spinal cord

↓

- Nerve root

⇒ Intervertebral disc

⇒ Intervertebral foramen

↓

- Nerve plexus (e.g. brachial plexus)

↓

- Peripheral nerve

⇒ Potential sites of nerve entrapment (e.g. carpal tunnel)

↓

× Muscle

CONDITION/S ASSOCIATED WITH

Common
- Muscle disuse (e.g. fracture, arthritis, immobility)
- Radiculopathy
- Peripheral neuropathy
- Peripheral vascular disease

Less common
- Cerebral infarction
- Cerebral haemorrhage
- Spinal cord injury
- Motor neuron disease
- Poliomyelitis

MECHANISM/S

Muscle atrophy is caused by:
1. lower motor neuron disorders
2. disuse atrophy
3. upper motor neuron disorders
4. myopathy
5. peripheral vascular disease.

Lower motor neuron disorders

Muscle denervation results in profound muscle atrophy. Loss of lower motor neuron input at the neuromuscular junction causes breakdown of actin and myosin, resulting in a decrease in cell size and involution of myofibrils.[31,32] Causes include radiculopathy, compression peripheral neuropathy (e.g. carpal tunnel syndrome) and hereditary peripheral neuropathy (e.g. Marie–Charcot–Tooth disease), and motor neuron disease (e.g. amyotrophic lateral sclerosis).

Disuse atrophy

Disuse atrophy is caused by decreased muscle utilisation following trauma (e.g. fracture and immobilisation) or in chronic painful conditions (e.g. arthritis). Muscle wasting is present in the distribution of immobilised muscles. Disuse atrophy is a physiological response to decreased muscle use, resulting in a reduction in muscle fibre size and decreased muscle volume.

Upper motor neuron disorders

In upper motor neuron lesions, the magnitude and rate of progression of muscle atrophy is less pronounced and slower in onset than in lower motor neuron lesions. Decreased tissue bulk may be related to decreased muscle utilisation due to the sequelae of upper motor neuron disease (e.g. spasticity, weakness).

Myopathy

Myopathies are an uncommon cause of muscle wasting. Myopathies predominantly affect the proximal muscle groups. In advanced muscular dystrophies (e.g. Duchenne's muscular dystrophy), muscle fibres undergo degeneration and are replaced by fibrofatty tissue and collagen.[31] This may also result in pseudohypertrophy as the disease progresses. Myotonic dystrophy, which, unlike other myopathies, primarily affects the musculature, is associated with distal muscle wasting in these muscle groups.

Peripheral vascular disease

Inadequate tissue perfusion to meet the metabolic demands of peripheral tissues (e.g. muscles) causes muscle fibre atrophy. The most common cause is atherosclerosis. Evidence of trophic changes due to inadequate tissue perfusion often coexist (e.g. poikilothermia, hair loss, skin ulceration).

SIGN VALUE

Pronounced muscle atrophy is most commonly a lower motor neuron sign. The distribution of muscle atrophy and associated features (e.g. upper motor neuron signs versus lower motor neuron signs) is important when considering aetiologies of muscle wasting (see also 'Weakness' in this chapter). Refer to Tables 5.3 and 5.4.

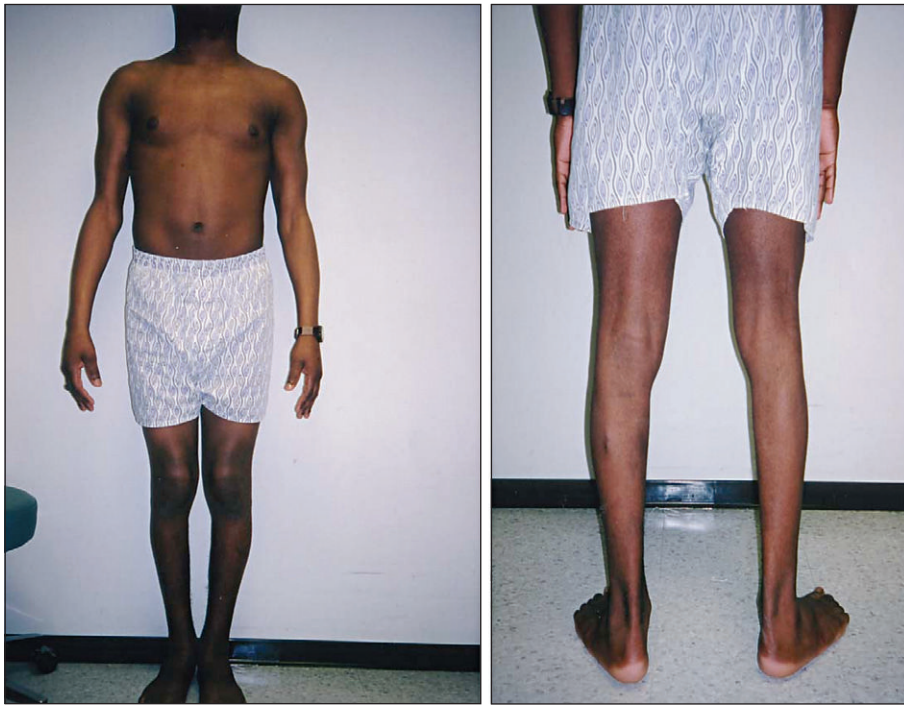


Figure 5.13 Left calf atrophy following acute poliomyelitis

Reproduced, with permission, from Bertorini TE, *Neuro-muscular Case Studies*, 1st edn, Philadelphia: Butterworth-Heinemann, 2007: Fig 76-1.

TABLE 5.3 Clinical utility of thenar atrophy in carpal tunnel syndrome

	Sensitivity	Specificity	Positive LR	Negative LR
Thenar atrophy[33–35]	4–28%	82–99%	NS	NS

Adapted from McGee S, *Evidence Based Physical Diagnosis*, 2nd edn, St. Louis: Saunders, 2007.

TABLE 5.4 Clinical utility of calf wasting in lumbosacral radiculopathy

	Sensitivity	Specificity	Positive LR	Negative LR
Ipsilateral calf wasting[36]	29%	94%	5.2	0.8

Adapted from McGee S, *Evidence Based Physical Diagnosis*, 2nd edn, St. Louis: Saunders, 2007.

Babinski response

DESCRIPTION

The Babinski response, or upgoing plantar response, is an abnormal cutaneous reflex response of the foot associated with upper motor neuron dysfunction.[4] In a positive Babinski response, scratching the lateral plantar surface of the patient's foot causes contraction of the extensor hallucis longus muscle and extension of the great toe (normally the toe goes down).[4]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

UPPER MOTOR NEURON

- Motor cortex

↓

- Corona radiata, subcortical white matter

↓

- Posterior limb, internal capsule

↓

- Corticospinal tracts, medial brainstem

↓

∅ Pyramidal decussation, medulla

↓

- Lateral corticospinal tracts, spinal cord

↓

CUTANEOUS REFLEX

→ Inhibitory interneuron
→ Sensory afferent neuron
→ Alpha motor neuron

CONDITION/S ASSOCIATED WITH[4]

Common

- Cerebral infarction
- Cerebral haemorrhage
- Spinal cord injury

Less common

- Lacunar infarction, posterior limb internal capsule
- Multiple sclerosis
- Mass lesion (e.g. tumour, abscess, AVM)

MECHANISM/S

Before 1 or 2 years of age, a noxious stimulus applied to the lower extremities causes involuntary ankle and foot dorsiflexion.[4] The so-called 'flexion response' is a primitive reflex that disappears later in life.[4] After 1 or 2 years of age, normal development of the central nervous system diminishes the flexion response, and the toes subsequently move downward (i.e., a normal plantar cutaneous reflex).[4,37] In a positive Babinski response, upper motor neuron dysfunction disrupts the normal plantar cutaneous reflex and the 'flexion response' re-emerges.[4] Upper motor neuron signs may coexist (e.g. spasticity, weakness, hyperreflexia). In the hyperacute period following upper motor neuron dysfunction, the Babinski response (as with spasticity and hyperreflexia) may be absent, as it may take hours or days for these signs to emerge.[38,39]

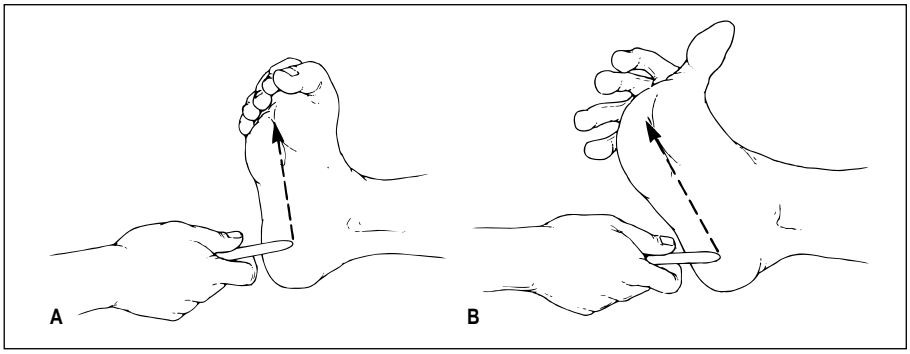


Figure 5.14 Babinski test

A, Downgoing or negative, normal; **B**, upgoing or positive Babinski response, abnormal.

Reproduced, with permission, from Benzon H et al, *Raj's Practical Management of Pain*, 4th edn, Philadelphia: Mosby, 2008: Fig 10-1.

SIGN VALUE

The Babinski sign is an upper motor neuron sign. It may be absent initially in the hyperacute period following upper motor neuron dysfunction. Refer to Table 5.5.

TABLE 5.5 Clinical utility of the Babinski test in patients with unilateral cerebral hemisphere lesion[38]

	Sensitivity	Specificity	Positive LR	Negative LR
Babinski response[40]	45%	98%	19.0	0.6

Adapted from McGee S, *Evidence Based Physical Diagnosis*, 2nd edn, St. Louis: Saunders, 2007.

Bradykinesia

DESCRIPTION

Bradykinesia is a slowness or poverty of movement.[41,42] Hypokinesia is a decreased ability to initiate a movement.[41,42] Bradykinesia and hypokinesia are associated with disorders of the basal ganglia. Weakness is not typically a prominent feature.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

BASAL GANGLIA

- Globus pallidus interna
- Globus pallidus externa
- Putamen
- Caudate nucleus
- Substantia nigra
- Subthalamic nuclei
- Striatum

CONDITION/S ASSOCIATED WITH[43]

Common

- Parkinson's disease
- Drugs – dopamine antagonists (e.g. haloperidol, metoclopramide)
- Diffuse white matter disease (e.g. lacunar infarction)

Less common

- Multisystem atrophy
- Progressive supranuclear palsy
- Corticobasilar degeneration

MECHANISM/S

The exact mechanism of bradykinesia is unknown. The direct and indirect pathways are theoretical models of the functional organisation of the basal ganglia. The direct pathway mediates initiation and maintenance of movement, and the indirect pathway functions to inhibit superfluous movement.[41,44] In general, degeneration of the substantia nigra or dopamine receptor antagonism causes inhibition of the direct pathway and potentiation of the indirect pathway. This results in net inhibition effects on the cortical pyramidal pathways and bradykinesia.[41,44] Associated signs of parkinsonism include resting tremor, rigidity and postural instability. Causes of bradykinesia include:

1. Parkinson's disease and the Parkinson's plus syndromes
2. dopamine antagonists.

Parkinson's disease and the Parkinson's plus syndromes

Parkinson's disease and the Parkinson's plus syndromes (e.g. multisystem atrophy, progressive supranuclear palsy,

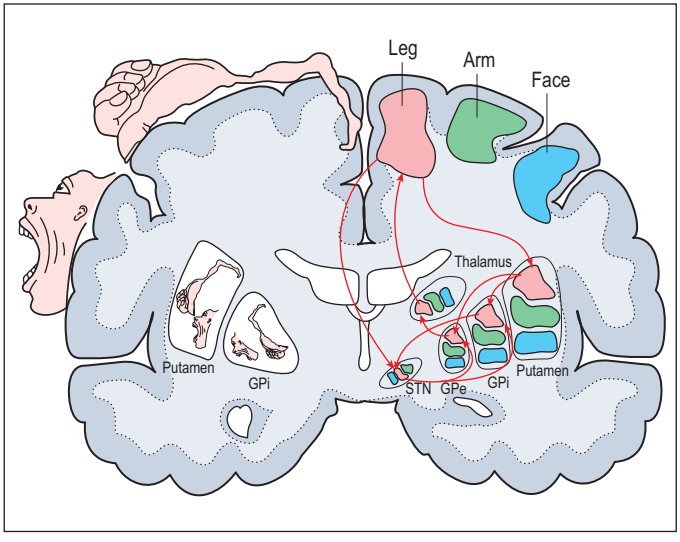


Figure 5.15 Basal ganglia motor circuit and somatotopic organisation

GPe = globus pallidus pars externa; GPi = globus pallidus pars interna; STN = subthalamic nucleus.

Reproduced, with permission, from Rodriguez-Oroz MC, Jahanshahi M, Krack P et al, Lancet Neurol 2009; 8: 1128–1139: Fig 2.

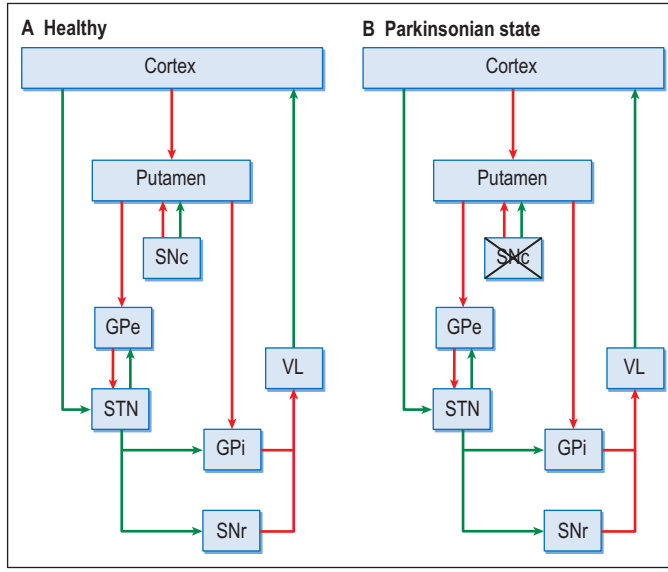


Figure 5.16 Classic pathophysiological model in parkinsonism

A Cortical motor areas project glutamatergic axons to the putamen, which sends gamma-aminobutyric acid (GABA)ergic projections to the GPi and the SNr by two pathways: the monosynaptic GABAergic 'direct pathway' (putamen–GPi) and the trisynaptic (putamen–GPe–STN–GPi/SNr) 'indirect pathway'. Dopamine from the SNc facilitates putaminal neurons in the direct pathway and inhibits those in the indirect pathway. Activation of the direct pathway causes reduced neuronal firing in the GPi/SNr and movement facilitation. Activation of the indirect pathway suppresses movements. The STN is also activated by an excitatory projection from the cortex called the 'hyperdirect pathway'. **B** Functional deficiency of dopamine also causes increased activity in the indirect pathway and hyperactivity of the STN. Functional dopamine deficiency also results in decreased activity of the indirect pathway. Together, these result in increased GPi/SNr output inhibition of the VL nucleus of the thalamus and reduced activation of cortical and brainstem motor regions.

GPe = globus pallidus pars externa; GPi = globus pallidus pars interna; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus; VL = ventrolateral nucleus, thalamus.

corticobasilar degeneration) are neurodegenerative diseases that affect the basal ganglia, as well as other neurological structures. Degeneration of the substantia nigra results in a deficiency of dopaminergic neurons supplying the putamen and causes a relative imbalance between the direct and indirect pathways.

Dopamine antagonists

Central-acting dopamine antagonists block the effect of dopamine in the putamen. Blocking dopaminergic receptors in the putamen causes dysfunction of the direct and indirect pathways.

SIGN VALUE

In one study, the sensitivity and specificity of bradykinesia in the diagnosis of Parkinson's disease (the gold standard assessment for Parkinson's disease was based on a post-mortem exam) were 90% and 3%, respectively.[45]

Broca's aphasia (expressive aphasia)

DESCRIPTION

Broca's aphasia, or expressive aphasia, is a disorder of speech fluency (i.e., word production). Comprehension is less affected (compare this with receptive aphasia or Wernicke's aphasia; see 'Wernicke's aphasia' in this chapter). Patients demonstrate speech that is laboured and short, lacks normal intonation, and is grammatically simple and monotonous.[6] Typically, phrase length is decreased and the number of nouns is out of proportion to the use of prepositions and articles (i.e., the 'content' words are present but the joining grammar and syntax may not be).[6,46]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[46]

- Broca's area – posterior inferior frontal gyrus, dominant hemisphere

⇒ Superior division, middle cerebral artery (MCA)

CONDITION/S ASSOCIATED WITH

Common

- MCA territory infarction, dominant hemisphere
- Cerebral haemorrhage, dominant hemisphere
- Vascular dementia

Less common

- Alzheimer's disease
- Mass lesion (e.g. tumor, abscess, AVM)
- Trauma
- Migraine
- Primary progressive aphasia

MECHANISM/S

Broca's aphasia is typically caused by a lesion in the posterior inferior frontal gyrus of the dominant hemisphere.[46,47] This region is supplied by branches of the superior division of the middle cerebral artery (MCA).[46] The most common cause is superior division MCA territory infarction. Patient hand dominance (i.e., being left- or right-handed) correlates with the side of the dominant cerebral hemisphere, and therefore has potential localising value (see also 'Hand dominance' in this chapter). Larger lesions may affect the motor and sensory cortex resulting in contralateral motor and sensory findings.[47] Associated motor and sensory findings are more commonly associated with Broca's aphasia, due to the proximity of the motor cortex to the vascular distribution of the superior division of the middle cerebral artery (see Table 5.6).[46]

SIGN VALUE

Broca's aphasia, or expressive aphasia, is a dominant cortical localising sign. Acute onset aphasia should be considered a sign of stroke until proven otherwise.

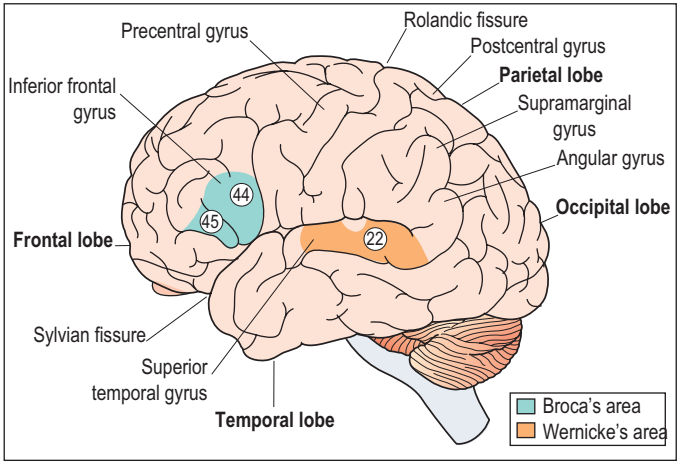


Figure 5.17 Broca's area: the posterior inferior frontal gyrus, dominant hemisphere

22 = Brodmann's area 22; 44 = Brodmann's area 44; 45 = Brodmann's area 45.

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn. Philadelphia: Butterworth-Heinemann, 2008: Fig 12A-1.

5

TABLE 5.6 Clinical features of Broca's aphasia

Clinical feature	Abnormality in Broca's aphasia
Spontaneous speech	• Nonfluent, mute or telegraphic • Dysarthria usually present
Naming	• Impaired
Comprehension	• Intact (mild difficulty with complex grammatical phrases)
Repetition	• Impaired
Reading	• Often impaired
Writing	• Impaired, dysmorphic, dysgrammatical
Associated signs	• Contralateral motor and sensory findings

Adapted from Kirshner HS, Language and speech disorders: aphasia and aphasiac syndromes. In: Bradley WG, Daroff RB, Fenichel G et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008.

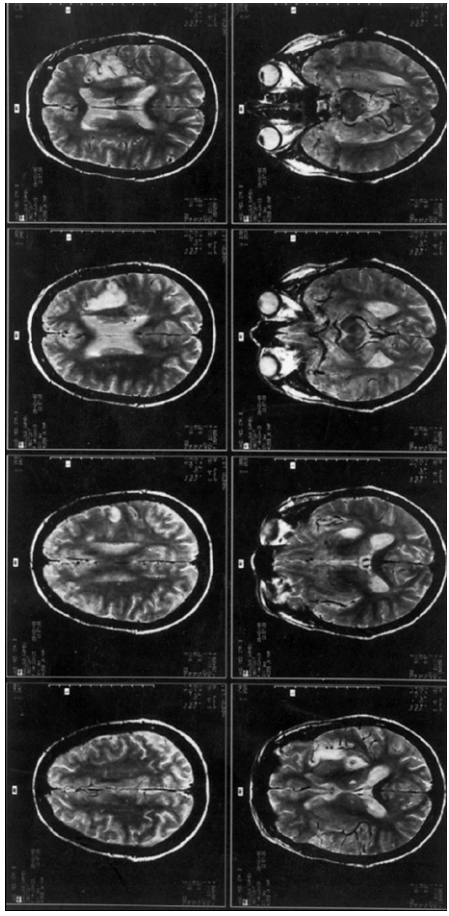


Figure 5.18 MRI imaging study in a patient with Broca's aphasia caused by infarction of Broca's area, subcortical white matter and the insula

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 12A-3.

Brown-Séquard syndrome

DESCRIPTION

Brown-Séquard syndrome is a rare clinical syndrome caused by spinal cord hemisection and is characterised by:[48]

- ipsilateral weakness below the lesion
- ipsilateral loss of light touch, vibration, proprioception sensation below the lesion
- contralateral loss of temperature and pain sensation below the lesion
- a narrow band of ipsilateral complete sensory loss at the level of the lesion.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

Spinal cord

DORSAL COLUMN PATHWAY

- • Dorsal columns
- ∅ Medial lemniscus, medulla

SPINOTHALAMIC TRACTS

- • Spinothalamic tracts
- ∅ White ventral commissure, spinal cord

MOTOR

- • Lateral corticospinal tract
- • Anterior horn grey matter

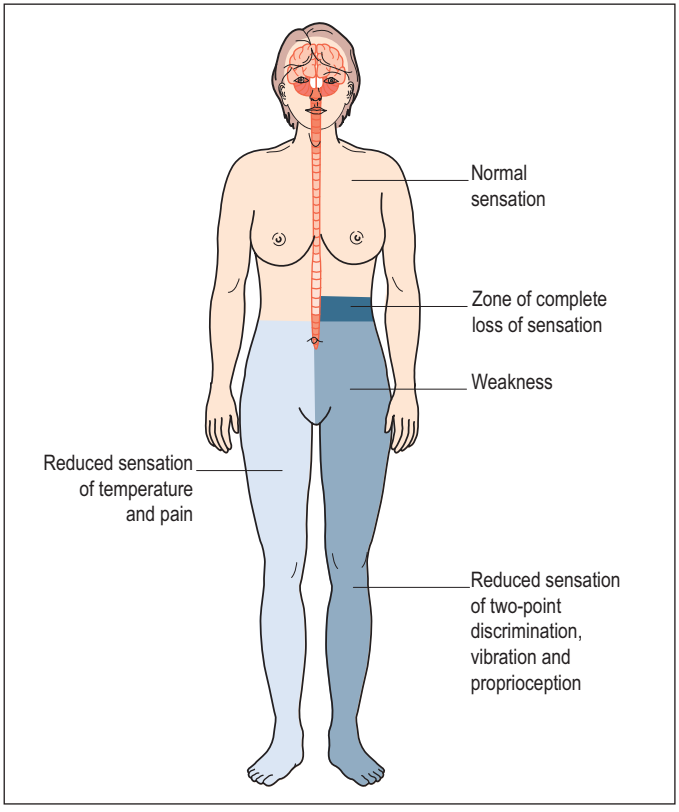


Figure 5.19 Distribution of motor and sensory findings in left-sided spinal cord hemisection (i.e., Brown-Séquard syndrome at approximately T8 spinal level)

Reproduced, with permission, from Purves D, Augustine GJ, Fitzpatrick D et al (eds), *Neuroscience*, 2nd edn, Sunderland (MA): Sinauer Associates, 2001: Fig 10.4.

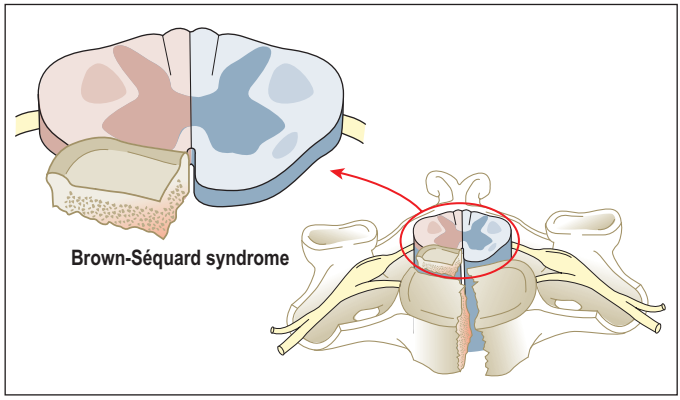


Figure 5.20 Schematic diagram of a lesion associated with Brown-Séquard syndrome due to burst fracture

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 54C-8.

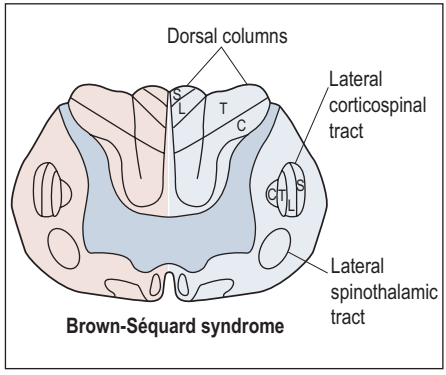


Figure 5.21 Neuroanatomy of the spinal cord long tracts and grey matter in Brown-Séquard syndrome

Reproduced, with permission, from Browner BD, *Skeletal Trauma*, 4th edn, Philadelphia: Saunders, 2008: Fig 25-7.

CONDITION/S ASSOCIATED WITH

Common

- Penetrating trauma
- Multiple sclerosis

Less common

- Epidural abscess
- Vertebral fracture
- Mass lesion (e.g. tumour, abscess, AVM)

MECHANISM/S

The mechanisms of clinical findings in Brown-Séquard syndrome are listed in Table 5.7 (see also Figure 5.21).

SIGN VALUE

Brown-Séquard syndrome is a rare clinical syndrome associated with spinal cord hemisection.

TABLE 5.7 Neuroanatomical mechanisms of Brown-Séquard syndrome

Clinical signs	Mechanism
• Ipsilateral weakness below the lesion • Upper motor neuron signs	→ Corticospinal tract lesion
• Ipsilateral loss of light touch, vibration, proprioception below the lesion	→ Dorsal column lesion
• Ipsilateral narrow band complete sensory loss at the level of the lesion, and 'sensory level'	→ Spinothalamic tract, dorsal column +/– posterior horn cells and sensory nerve root lesion
• Contralateral loss of pain and temperature sensation below the lesion	→ Spinothalamic tract lesion (*Note*: Lesion is above decussation at each spinal level, thus deficitis are contralateral below the lesion)

Cavernous sinus syndrome

DESCRIPTION

Cavernous sinus syndrome represents multiple cranial nerve abnormalities due to damage of the nerves of the cavernous sinus (e.g. oculomotor nerve (CNIII), trochlear nerve (CNIV), ophthalmic division of the trigeminal nerve (CNV V1), maxillary division of the trigeminal neve (CNV V2), abducens nerve (CNVI) and sympathetic fibres).[6]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[6]

CAVERNOUS SINUS CONTENTS:

- Oculomotor nerve (CNIII)
- Trochlear nerve (CNIV)
- Ophthalmic division (V1) trigeminal nerve (CNV)
- Abducens nerve (CNVI)
- Sympathetic plexus
- ⇒ Venous plexus
- ⇒ Carotid artery
- ⇒ Pituitary gland
- ⇒ Sphenoid sinus
- ⇒ Ethmoid sinus

CONDITION/S ASSOCIATED WITH[6,49]

Common

- Septic thrombosis
- Aseptic thrombosis
- Tolosa–Hunt syndrome

Less common

- Cavernous carotid artery aneurysm
- Rhinocerebral mucormycosis
- Pituitary apoplexy
- Cavernous–carotid sinus fistula

MECHANISM/S

The cavernous sinus is crowded with neural and vascular structures (see Table 5.8) and is located in close proximity to the pituitary gland and ethmoid and sphenoid sinuses. Associated findings include unilateral periorbital oedema, photophobia, proptosis, papilloedema, retinal haemorrhages and decreased visual acuity.[49] Causes of cavernous sinus syndrome include:[1,50,51]

1. septic thrombosis
2. aseptic thrombosis
3. cavernous internal carotid artery aneurysm
4. pituitary apoplexy
5. disorders of the sphenoid and ethmoid sinuses.

Septic thrombosis

The most common sources of septic thrombosis are infective foci of the sphenoid or ethmoid sinuses.[49] Other sources include dental infection, central facial cellulitis and otitis.[49] Infectious organisms enter the cavernous sinus through venous and lymphatic vessels from the surrounding ocular and facial structures or via direct spread from adjacent tissues.

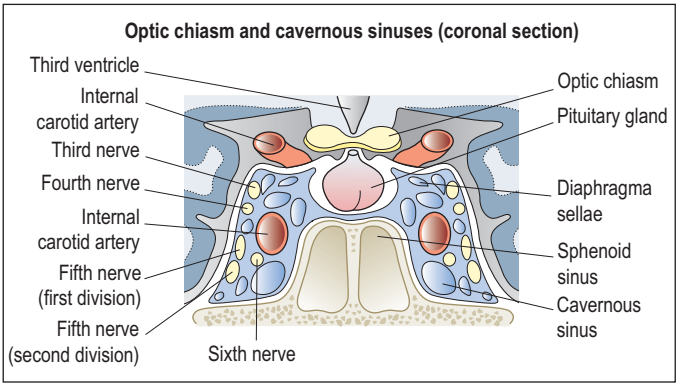


Figure 5.22 Contents of the cavernous sinus

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 9-11-3.

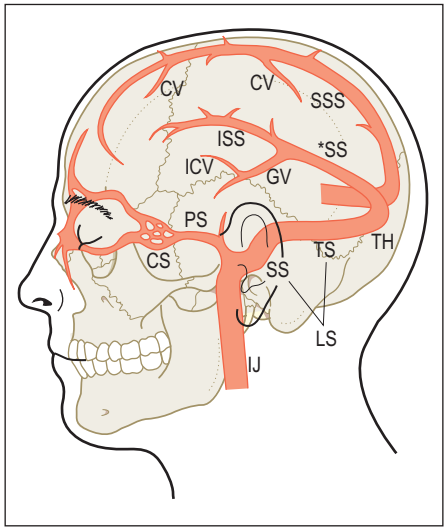


Figure 5.23 Venous drainage of the intracranial structures

CS = cavernous sinus; CV = cortical veins; GV = great vein of Galen; ICV = internal cerebral vein; IJ = internal jugular vein; ISS = inferior sagittal sinus; LS = lateral sinus; PS = petrosal sinus; SS = sigmoid sinus; *SS = straight sinus; SSS = superior sagittal sinus; TH = torcular Herophili; TS = transverse sinus.

Reproduced, with permission, from Goldman L, Ausiello D, *Cecil Medicine*, 23rd edn, Philadelphia: Saunders, 2007: Fig 430-6.

Aseptic thrombosis

Aseptic thrombosis is less common than septic thrombosis and is associated with hypercoagulable states (e.g. polycythaemia, sickle cell disease, trauma, pregnancy and oral contraceptive use).[49]

Cavernous internal carotid artery aneurysm

Expansion of a cavernous internal carotid artery aneurysm can result in injury due to mass effect. The abducens nerve (CNVI) is typically affected early, due to its close proximity to the cavernous segment of the internal carotid artery.[1]

Pituitary apoplexy[49]

Pituitary apoplexy is acute haemorrhage into a pre-existing pituitary macroadenoma, which causes compression or injury to the surrounding tissues. Pituitary apoplexy is also associated with bitemporal hemianopia due to compression of the optic chiasm. Risk factors include hypotension, stimulation of gland growth (e.g. pregnancy), anticoagulation and hyperaemia.[50]

Disorders of the sphenoid and ethmoid sinuses

Acute and chronic erosive inflammatory conditions of the sphenoid and ethmoid sinuses may lead to contiguous spread of

TABLE 5.8 Neuroanatomical mechanism of cavernous sinus syndrome

Clinical signs	Nerve dysfunction
• Extraocular muscle weakness – all muscles except SO, LR • Mydriasis and poorly reactive pupil • Ptosis	→ Oculomotor nerve (CNIII)
• Superior oblique muscle weakness	→ Trochlear nerve (CNIV)
• Hyperaesthesia or anaesthesia in the distribution of the ophthalmic nerve and/or maxillary nerve • Decreased corneal sensation • Decreased corneal reflex	→ Ophthalmic branch trigeminal nerve (CNV V1) → Maxillary branch trigeminal nerve (CNV V2)
• Lateral rectus muscle weakness	→ Abducens nerve (CNVI)
• Horner's syndrome	→ Sympathetic fibres

SO = superior oblique muscle; LR = lateral rectus muscle.

an infectious or inflammatory process to the adjacent cavernous sinus (refer to Figure 5.22). Causes include bacterial sinusitis, mucormycosis, Tolosa–Hunt syndrome and tumours.[49]

SIGN VALUE

Cavernous sinus syndrome is an emergency and has a high rate of morbidity and mortality.

Clasp-knife phenomenon

DESCRIPTION

Clasp-knife phenomenon is characterised by brisk relaxation of hypertonic muscle groups during passive range of motion testing.[52] The name arises from the similarity of the phenomenon to opening and closing the blade of a pocket knife due to the action of the spring.[4,53]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

UPPER MOTOR NEURON

- Motor cortex

↓

- Corona radiata, subcortical white matter

↓

- Posterior limb, internal capsule

↓

- Corticospinal tracts, medial brainstem

↓

∅ Pyramidal decussation, medulla

↓

- Corticospinal tracts, spinal cord

⇒ Central canal, spinal cord

↓

MONOSYNAPTIC STRETCH REFLEX

→ Inhibitory interneuron

→ Sensory afferent neuron

→ Alpha motor neuron

CONDITION/S ASSOCIATED WITH

Common

- Cerebral infarction
- Cerebral haemorrhage
- Cerebral palsy

Less common

- Multiple sclerosis
- Myelopathy
- Mass lesion (e.g. tumour, abscess, AVM)

MECHANISM/S

The mechanism of clasp-knife phenomenon is unknown. It is associated with upper motor neuron dysfunction and spasticity. It is thought to arise due to inappropriate activity of muscles spindles and extrafusal muscle fibres due to loss of inhibitor supraspinal pathways.[54]

SIGN VALUE

Clasp-knife phenomenon is an upper motor neuron sign and is present in approximately 50% of patients with spasticity.[55,56]

Clonus

DESCRIPTION

Clonus is a rhythmic sustained muscular contraction brought on when the examiner briskly sustains a stretching force in a muscle group.[4] Clonus is most commonly elicited in the ankle by abrupt sustained dorsiflexion. It can also be assessed in other locations, such as the quadriceps, finger flexors, jaw and other muscle groups.[4]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

UPPER MOTOR NEURON
- Motor cortex

↓

- Corona radiata, subcortical white matter

↓

- Posterior limb, internal capsule

↓

- Corticospinal tracts, medial brainstem

↓

∅ Pyramidal decussation, medulla

↓

- Corticospinal tracts, spinal cord

⇒ Central canal, spinal cord

↓

MONOSYNAPTIC STRETCH REFLEX

→ Inhibitory interneuron

→ Sensory afferent neuron

→ Alpha motor neuron

CONDITION/S ASSOCIATED WITH

Common

- Cerebral infarction
- Cerebral haemorrhage
- Lacunar infarction, posterior limb internal capsule
- Multiple sclerosis
- Spinal cord injury

Less common

- Mass lesion (e.g. tumour, abscess, AVM)
- Serotonin syndrome

MECHANISM/S

Clonus is a sign of hyperreflexia in upper motor neuron dysfunction. Clonus is caused by a self-sustaining, oscillating, monosynaptic stretch reflex.[4,57] Causes of clonus include:

1. upper motor neuron lesion
2. serotonin syndrome.

Upper motor neuron lesion

See 'Hyperreflexia' in this chapter.

Serotonin syndrome

Serotonin syndrome is characterised by altered mental status, autonomic dysfunction and neuromuscular excitability.[58] The mechanism of clonus in serotonin syndrome is not known. Clonus likely results from an excessive agonism of 5-HT receptors in the peripheral nervous system, resulting in sensitisation of monosynaptic stretch reflexes.[59]

SIGN VALUE

Clonus is most commonly a sign of upper motor neuron dysfunction.

Cogwheel rigidity

DESCRIPTION

Cogwheel rigidity is resistance to a passive range of movement of a joint, which intermittently gives way like a lever pulling over a rachet.[4,60] Rigidity is a sign of extrapyramidal dysfunction.

Rigidity has three characteristics:[4,60]

1. Resistance is velocity-independent (i.e., the degree of resistance to passive movement is constant with slow or fast movement).
2. Flexor and extensor tone are equal.
3. There is no associated weakness.

See also 'Rigidity' in this chapter.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

BASAL GANGLIA

- Globus pallidus pars interna
- Globus pallidus pars externa
- Putamen
- Caudate nucleus
- Substantia nigra
- Subthalamic nuclei
- Striatum

CONDITION/S ASSOCIATED WITH

Common

- Parkinson's disease
- Drugs – dopamine antagonists (e.g. haloperidol, metoclopramide)
- Diffuse white matter disease (e.g. lacunar infarction)

Less common

- Multisystem atrophy
- Progressive supranuclear palsy
- Corticobasal degeneration

MECHANISM/S

Cogwheel rigidity is a type of rigidity associated with extrapyramidal disorders.[6,60] The mechanism of cogwheel rigidity is poorly understood. Cogwheel rigidity has been attributed to the combined effects of rigidity and tremor (see also 'Bradykinesia' and 'Parkinsonian tremor' in this chapter).[6,60] Rigidity likely results from changes in extrapyramidal regulation of supraspinal motor neurons and changes in spinal cord motor neuron activity in response to peripheral stimulation in stretch reflexes (see also 'Rigidity' in this chapter).[44]

SIGN VALUE

Cogwheel rigidity is a sign of extrapyramidal dysfunction. It is most commonly associated with Parkinson's disease.

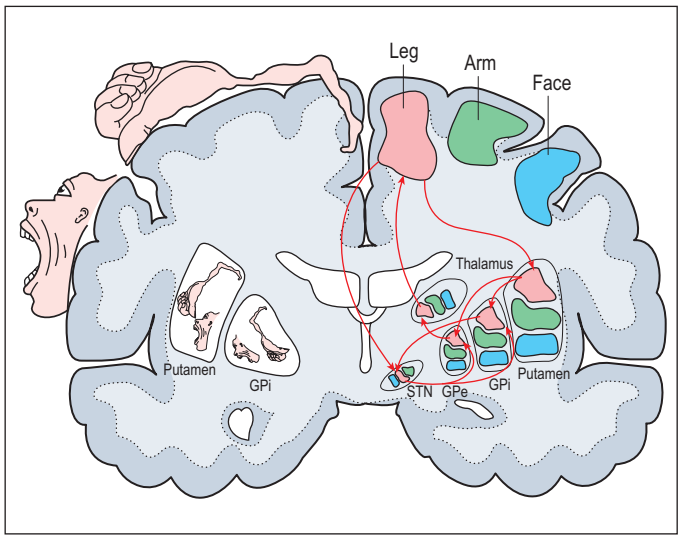


Figure 5.24 Basal ganglia motor circuit and somatotopic organisation

GPe = globus pallidus pars externa; GPi = globus pallidus pars interna; STN = subthalamic nucleus.

Reproduced, with permission, from Rodriguez-Oroz MC, Jahanshahi M, Krack P et al, Lancet Neurol 2009; 8: 1128–1139: Fig 2.

Corneal reflex

DESCRIPTION

When the cornea is stimulated with a wisp of cotton, there is a reflexive blinking response in both eyes (i.e., a normal response). An abnormal corneal reflex is either an:

- afferent defect – absence of bilateral blinking, due to ophthalmic division of the trigeminal nerve (CNV V1) dysfunction
- efferent defect – absence of unilateral blinking, due to facial nerve (CNVII) palsy.

In the clinical test, a wisp of cotton is applied from the side to prevent a 'blink to threat' response, which is mediated by visual cues (CNII) and thus may confound the examination.

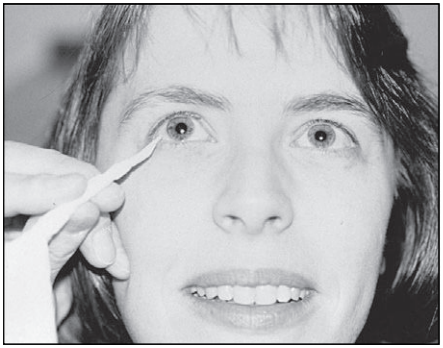


Figure 5.25 Corneal reflex

Reproduced, with permission, from University of California, San Diego, A Practical Guide to Clinical Medicine. Available: http://meded.ucsd.edu/clinicalmed/neuro2.htm [8 Dec 2010].

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[1,49]

AFFERENT LIMB

⊗ Light touch receptor, cornea

↓

• Long ciliary nerves

↓

• Ophthalmic division (V1) trigeminal nerve (CNV)

⇒ Orbital apex

⇒ Cavernous sinus

⇒ Superior orbital fissure

↓

• Trigeminal (gasserian) ganglion

⇒ Meckel's cave, petrous bone

↓

• Trigeminal sensory nucleus, pons

↓

↔ Bilateral innervation efferent structures

↓

EFFERENT LIMB

• Facial nuclei

↓

• Facial nerve

⇒ Cerebellopontine angle

⇒ Internal acoustic meatus

⇒ Mastoid sinus

⇒ Geniculate ganglion

⇒ Stylomastoid foramen

↓

× Orbicularis oculi muscles

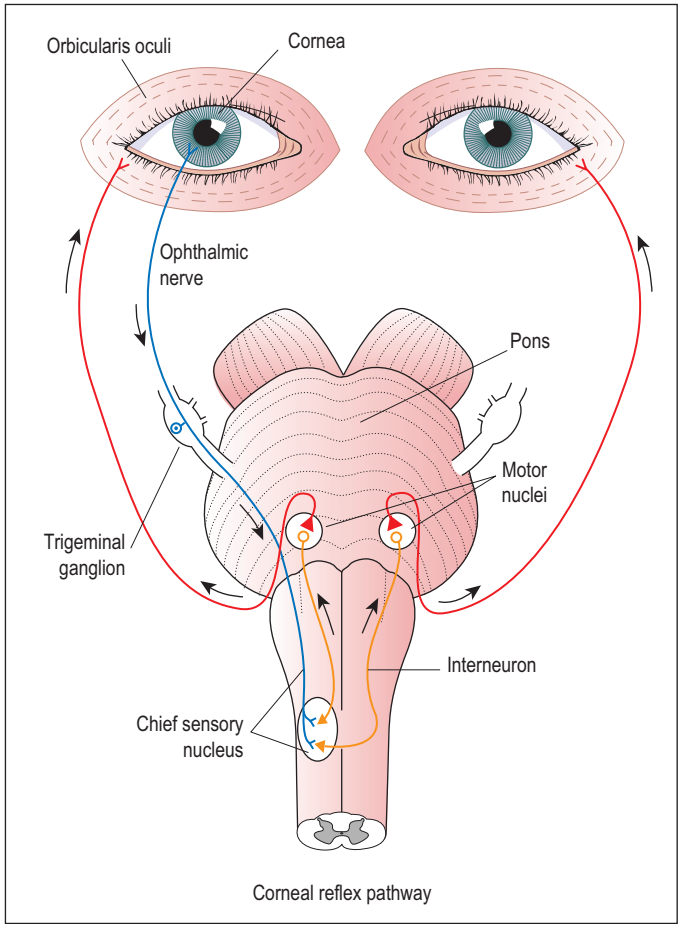


Figure 5.26 Corneal reflex pathway

Normally, lightly touching the cornea results in bilateral blinking. The afferent limb is the ophthalmic division of the trigeminal nerve (CNV V1). The efferent limb is the facial nerve (CNVII), which innervates the orbicularis oculi muscles.

Reproduced, with permission, from O'Rahilly R, Muller F, Carpenter F, *Basic Human Anatomy: A Study of Human Structure*. Philadelphia: Saunders, 1983: Fig 46-8.

CONDITION/S ASSOCIATED WITH

Common

- Bell's palsy (idiopathic facial nerve palsy)
- Facial nerve palsy
- Coma

Less common

- Cerebellopontine angle tumor (e.g. acoustic schwannoma)
- Cavernous sinus syndrome

MECHANISM/S

The afferent limb of the corneal reflex is supplied by the ophthalmic division of the trigeminal nerve (CNV V1), and the efferent motor limb is supplied by the facial nerve (CNVII), which innervates the orbicularis oculi muscles. Absence of the corneal reflex may be due to a defect in the afferent or efferent pathway. Lesions of the afferent pathway result in a bilateral absence of the blinking response when the abnormal eye is tested with cotton wool. Lesions of the efferent limb will cause an absent blinking response on the affected side, with preservation of the blinking response on the contralateral side. Causes of an absent corneal reflex include:

1. facial nerve palsy
2. disorders of the ophthalmic division of the trigeminal nerve (CNV V1)
3. disorders of the cornea.

Facial nerve palsy

See 'Facial muscle weakness' in this chapter.

Disorders of the ophthalmic division of the trigeminal nerve (CNV V1)

Disorders of the ophthalmic division of the trigeminal nerve include orbital apex syndrome, cavernous sinus syndrome,

superior orbital fissure stenosis and mass lesions (e.g. tumour, abscess) affecting the nerve segment spanning the subarachnoid space. See also 'Orbital apex syndrome' and 'Cavernous sinus syndrome' in this chapter.

Disorders of the cornea

Disorders of the cornea causing dysfunction of the neurosensory elements of the long ciliary nerves may result in an afferent defect in the corneal reflex. Causes include trauma, contact lens desensitisation, globe rupture and topical analgesic agents (e.g. proxymetacaine).

SIGN VALUE

Corneal reflex testing may be useful in unilateral sensorineural hearing loss and unilateral facial weakness, and in the assessment of gross brainstem function. The corneal reflex has been reported to be absent in 8% of normal elderly patients in one study.[4,61] In a single study, the sensitivity of an efferent abnormality of the corneal reflex in the detection of acoustic neuroma (i.e., acoustic schwannoma) was 33%.[4,62]

Crossed-adductor reflex

DESCRIPTION

Adductor muscle contraction of the leg occurs following percussion of the contralateral medial femoral condyle, patella or patella tendon.[4,63] It is a radiating reflex and a sign of hyperreflexia.

CONDITION/S ASSOCIATED WITH

Common

- Cerebral infarction
- Cerebral haemorrhage
- Lacunar infarction, posterior limb internal capsule

Less common

- Multiple sclerosis
- Spinal cord injury
- Mass lesion (e.g. tumour, abscess, AVM)

MECHANISM/S

The force of the reflex hammer is conducted through bone and soft tissues to distant hyperreflexic muscles, eliciting a stretch reflex-mediated contraction of the adductor muscles on the opposite side (see 'Hyperreflexia' in this chapter).[4]

SIGN VALUE

The cross-adductor reflex, like other radiating reflexes, is a sign of hyperreflexia in upper motor neuron dysfunction.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

UPPER MOTOR NEURON

- Motor cortex

↓

- Corona radiata, subcortical white matter

↓

- Posterior limb, internal capsule

↓

- Corticospinal tracts, medial brainstem

↓

∅ Pyramidal decussation, medulla

↓

- Corticospinal tracts, spinal cord

⇒ Central canal, spinal cord

↓

MONOSYNAPTIC STRETCH REFLEX

→ Inhibitory interneuron

↓

→ Sensory afferent neuron → Alpha motor neuron

Dysarthria

DESCRIPTION

Dysarthria is a disorder of speech articulation. Comprehension and speech content are not affected. There are several types of dysarthria that vary in the rate, volume, rhythm and sound of the patient's speech (see Table 5.9).[64–66]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

- Cerebellum
- Upper motor neuron
- Lower motor neuron

CONDITION/S ASSOCIATED WITH

Common

- Alcohol misuse
- Cerebellar infarction
- Cerebellar haemorrhage
- Drugs – benzodiazepine, lithium

Less common

- Hereditary cerebellar degeneration (e.g. Freidreich's ataxia)
- Head and neck neoplasia
- Paraneoplastic cerebellar degeneration

MECHANISM/S

Dysarthria is caused by disorders of the:

1. cerebellum
2. oral cavity and oropharynx
3. upper motor neuron
4. lower motor neuron.

Disorders of the cerebellum

Cerebellar dysfunction disrupts coordination of the muscles of articulation resulting in slurred speech, explosive speech or speech that is broken up into syllables with noticable pauses (i.e., staccato speech or scanning speech).[66] Common causes include alcohol misuse, cerebellar infarction, multiple sclerosis and hereditary cerebellar degeneration.

Disorders of the oral cavity and oropharynx

Local disorders of the oral cavity and oropharynx disrupt the transmission of sound waves through the oral cavity, resulting in 'slurred' speech. The rate and rhythm of speech are typically not affected. Common causes include trauma and neck neoplasia and iatrogenic causes (e.g. local anaesthesia).

Disorders of the upper motor neuron

Dysarthria due to disease of the upper motor neuron is uncommon, but may be present in diffuse bilateral upper motor neuron disease. Spasticity of the muscles of speech articulation disrupts the normal mechanical properties of the oropharyngeal structures during speech. Causes include advanced degenerative cortical diseases (e.g. advanced Alzheimer's disease, vascular dementia), diffuse subcortical white matter disease (e.g. lacunar infarction), multiple sclerosis and cerebral palsy.

TABLE 5.9 Characteristics of dysarthria subtypes

Dysarthria subtype	Characteristics
Flaccid dysarthria	• Speech may sound nasal or slurred[65,66]
Spastic dysarthria	• Speech may sound as if patient is squeezing out words from a pursed mouth[65,66]
Ataxic dysarthria	• Speech is uncoordinated; range, timing and direction may be inaccurate; rate is slow; may be explosive in quality[65,66]
Hypokinetic dysarthria	• Speech may sound monotonous, or slow-paced; rate may vary; rigidity may be present[65,66]
Hyperkinetic dysarthria	• Involuntary disruptions in sounds and/or movements[65,66]

Disorders of the lower motor neuron

Dysfunction of the lower motor neuron results in hypotonia and weakness of the muscles of speech articulation. Common causes include facial nerve palsy.

SIGN VALUE

Dysarthria is a sign of cerebellar dysfunction, but may be present in a variety of other conditions. In a group of 444 patients with unilateral cerebellar lesions, dysarthria was found in approximately 10–25% of cases.[4,29,30]

Dysdiadochokinesis

DESCRIPTION

Dysdiadochokinesis is difficulty in performing rapid alternating movements. The patient's movements may be slow and/or clumsy.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

CEREBELLUM
- Intermediate cerebellar hemisphere
- → Lateral corticospinal tract
- → Rubrospinal tract
- Lateral cerebellar hemisphere
- → Lateral corticospinal tract

BASAL GANGLIA
- Globus pallidus interna
- Globus pallidus externa
- Putamen
- Substantia nigra
- Striatum

CONDITION/S ASSOCIATED WITH

Common

- Alcohol misuse
- Cerebellar infarction
- Cerebellar haemorrhage
- Drugs (e.g. benzodiazepine, lithium, phenytoin)

Less common

- Multiple sclerosis
- Hereditary cerebellar degeneration (e.g. Freidreich's ataxia)
- Mass lesion (e.g. tumour, abscess, AVM)
- Paraneoplastic cerebellar degeneration

MECHANISM/S

Dysdiadochokinesis is an ipsilateral hemispheric cerebellar sign. The intermediate and lateral hemispheres of the cerebellum mediate coordinated movements of the distal extremities (see Table 5.10). Lesions of the intermediate and lateral cerebellar hemispheres cause slow,

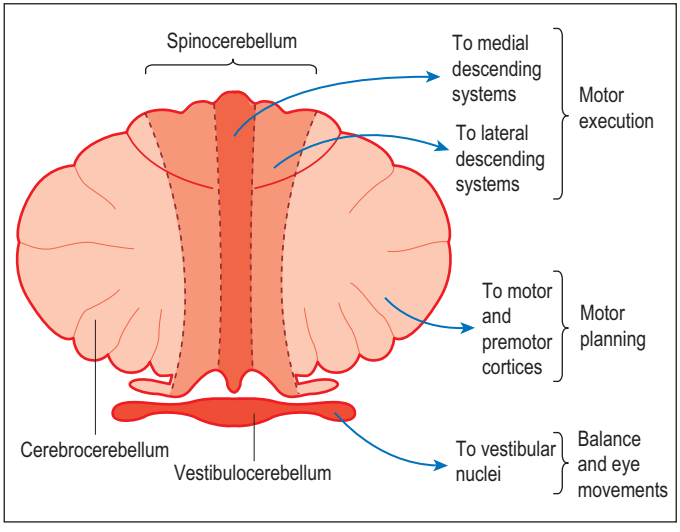


Figure 5.27 Functional anatomy of the cerebellum

Reproduced, with permission, from Barrett KE, Barman SM, Boitano S et al. *Ganong's Review of Medical Physiology*, 23rd edn. Available: http://accessmedicine.com [9 Dec 2010].

TABLE 5.10 Functional anatomy of the cerebellum and associated motor pathways

Cerebellar anatomy	Function	Associated motor pathways
Intermediate hemisphere	• Distal limb coordination	• Lateral corticospinal tracts • Rubrospinal tracts
Lateral hemisphere	• Motor planning, distal extremities	• Lateral corticospinal tracts

Adapted from Blumenfeld H, *Neuroanatomy Through Clinical Cases*, Sunderland: Sinauer, 2002.

uncoordinated and clumsy movements of the ipsilateral distal extremities during attempted rapid alternating movements.[4,6,29,67] Intermediate and lateral hemisphere dysfunction results in delays of motor initiation and movement termination at the end of movement (i.e., dysmetria). This, combined with abnormalities of movement force and acceleration, contribute to dysdiadochokinesia.[67]

SIGN VALUE

In a group of 444 patients with unilateral cerebellar lesions, dysdiadochokinesis was present in 47–69% of patients.[4,29,30]

Dysmetria

DESCRIPTION

Dysmetria is a disturbance of the rate, range and force of movement of the extended limb as it approaches a target.[4,6,68] Dysmetria is elicited during the finger-to-nose and heel-to-shin tests.[6]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

- Intermediate cerebellar hemisphere
  → Lateral corticospinal tract
  → Rubrospinal tract
- Lateral cerebellar hemisphere
  → Lateral corticospinal tract

CONDITION/S ASSOCIATED WITH

Common

- Alcohol misuse
- Cerebellar infarction
- Cerebellar haemorrhage
- Multiple sclerosis
- Drugs – benzodiazepine, lithium, phenytoin

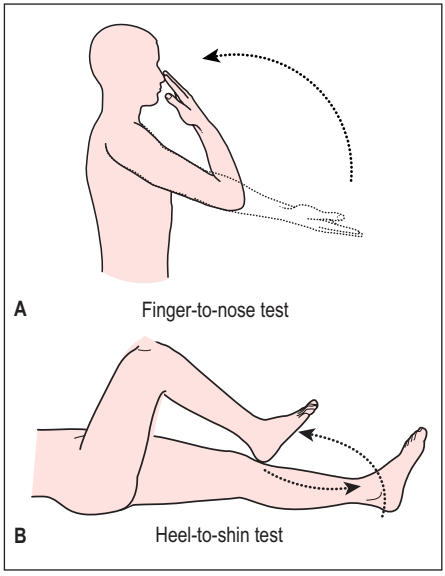


Figure 5.28 **A**, Finger-to-nose test; **B**, heel-to-shin test

Reproduced, with permission, from LeBlond RF, DeGowin RL, Brown DD, *DeGowin's Diagnostic Examination*, 9th edn. Available: http://www.accessmedicine.com [8 Dec 2010].

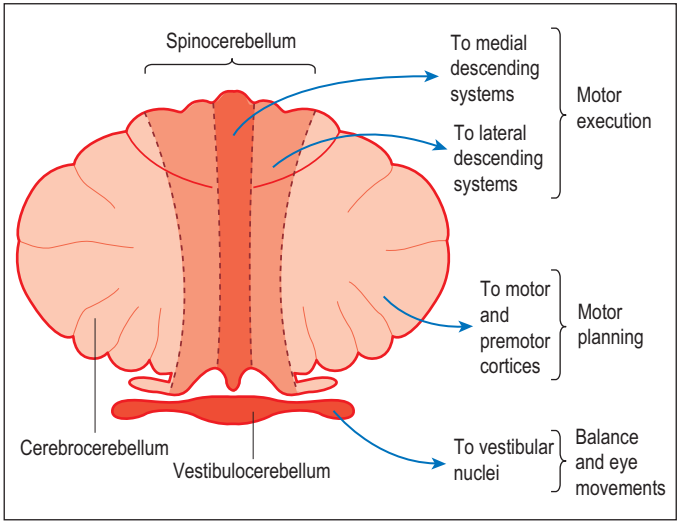


Figure 5.29 Functional anatomy of the cerebellum

Reproduced, with permission, from Barrett KE, Barman SM, Boitano S et al. *Ganong's Review of Medical Physiology*, 23rd edn. Available: http://accessmedicine.com [9 Dec 2010].

Less common

- Mass lesion (e.g. tumour, abscess, AVM)
- Hereditary cerebellar degeneration (e.g. Friedreich's ataxia)
- Paraneoplastic cerebellar degeneration

MECHANISM/S

Dysmetria is an ipsilateral hemispheric cerebellar sign. The intermediate and lateral hemispheres of the cerebellum facilitate coordinated movement of the distal extremities (see Table 5.11). Lesions of the intermediate and lateral cerebellar hemispheres may cause slow, uncoordinated and clumsy movements of the ipsilateral distal extremity during attempted target localisation tasks.[4] Delays in motor initiation and movement termination, and abnormalities of movement force and acceleration, contribute to dysmetria.[67]

SIGN VALUE

In a group of 444 patients with unilateral cerebellar lesions, dysmetria was present in 71–86% of patients.[4,29,30]

TABLE 5.11 Functional anatomy of the cerebellum and associated motor pathways

Cerebellar anatomy	Function	Associated motor pathways
Intermediate hemisphere	• Distal limb coordination	• Lateral corticospinal tracts • Rubrospinal tracts
Lateral hemisphere	• Motor planning, distal extremities	• Lateral corticospinal tracts

Dysphonia

DESCRIPTION

Dysphonia is a disorder of phonation (i.e., sound production) due to dysfunction of the larynx and/or vocal cords.[69] The patient's voice may sound hoarse, weak, excessively breathy, harsh or rough.[69]

CONDITION/S ASSOCIATED WITH[6,69,70]

Common

- Viral laryngitis
- Vocal cord polyp
- Iatrogenic (e.g. prolonged endotracheal intubation)

Less common

- Tumour (e.g. squamous cell carcinoma)
- Recurrent laryngeal nerve palsy (e.g. iatrogenic, Pancoast's tumour, penetrating neck trauma, thoracic aortic aneurysm)
- Laryngospasm
- Lateral medullary syndrome (Wallenberg's syndrome)

MECHANISM/S

Dysphonia is due to an abnormality within the larynx, vocal cords or the nerves that innervate these structures, which results in disruption of sound production due to changes in the mechanical function of the larynx and vocal cords.

Causes of dysphonia include:

1. local disorders of the vocal cords and larynx
2. disorders of the glossopharyngeal nerve, vagus nerve and recurrent laryngeal nerve.
3. brainstem lesion.

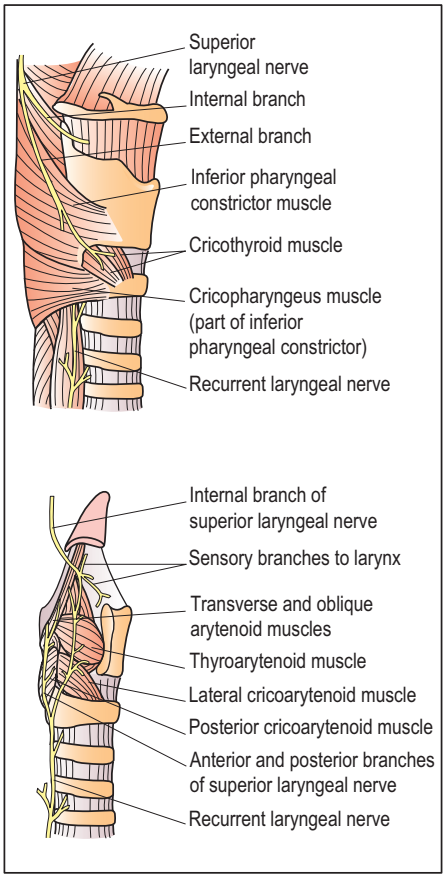
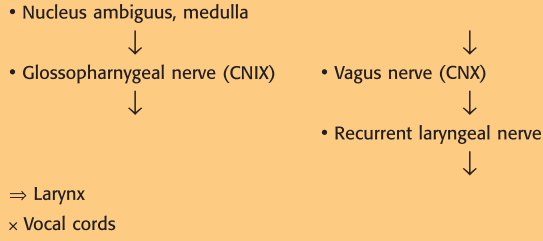


Figure 5.30 Anatomy and innervation of the laryngeal muscles and vocal cords

Reproduced, with permission, from Townsend CM, Beauchamp RD, Evers BM, Mattox K, *Sabiston Textbook of Surgery*, 18th edn, Philadelphia: Saunders, 2008: Fig 41-13.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[6]



Local disorders of the vocal cords and larynx

Mechanical disruption of vocal cord opposition, vibration or movement causes a change in sound generation. Common causes include viral laryngitis, vocal cord polyp, neoplasia (e.g. squamous cell carcinoma), trauma and iatrogenic (e.g. prolonged endotracheal intubation).

Disorders of glossopharyngeal nerve, vagus nerve and recurrent laryngeal nerve

The recurrent laryngeal nerve follows a long intrathoracic course and is vulnerable to compression or injury at several sites (e.g. Pancoast's tumour, penetrating neck trauma, thoracic aortic aneurysm, left atrial dilatation, iatrogenic injury in thyroidectomy).[6] Disorders of the glossopharyngeal nerve and vagus nerve may result in hoarseness due to a lesion involving cranial nerve nuclei or nerve fascicles (e.g. lateral medullary syndrome) or a lesion of the cranial nerve at the brainstem exit point (e.g. glomus tumour). See also 'Hoarseness' in this chapter.

Disorders of the brainstem

See 'Wallenberg's syndrome' in this chapter.

SIGN VALUE

Dysphonia can be an important sign of recurrent laryngeal nerve, vagus nerve (CNX) or nucleus ambiguus dysfunction, but is most commonly associated with viral laryngitis. Dysphonia should be interpreted in the context of the overall clinical findings. Isolated dysphonia that lasts longer than 2 weeks is unlikely to be caused by viral laryngitis and should prompt further evaluation.[70]

Essential tremor

DESCRIPTION

Essential tremor is typically a 4- to 12-Hz symmetric tremor of the upper limbs, with postural (i.e., seen in the outstretched arm) and/or kinetic (i.e., during movement) components.[4,41] It may also affect the jaw, tongue and head and neck muscles, leading to a characteristic 'nodding yes' or 'shaking no' tremor.[4]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

CEREBELLUM

- Vermis and flocculonodular lobe
  - → Anterior corticospinal tract
  - → Reticulospinal tract
  - → Vestibulospinal tract
  - → Tectospinal tract
- Paravermal (intermediate) hemisphere
  - → Lateral corticospinal tract
  - → Rubrospinal tract
- Lateral hemisphere
  - → Lateral corticospinal tract

CONDITION/S ASSOCIATED WITH[4,41]

Common

- Familial essential tremor

Less common

- Sporadic essential tremor

MECHANISM/S

The mechanism of essential tremor is not known. Essential tremor may originate from dysfunction of the cerebellum.[41] Approximately two-thirds of patients have a positive family history of tremor, and first-degree relatives of patients with essential tremor are 5 to 10 times more likely to develop the disease.[41] Several genetic loci have been identified in hereditary essential tremor.[41]

SIGN VALUE

Essential tremor has a relatively benign natural history and should be differentiated from other forms of tremor.

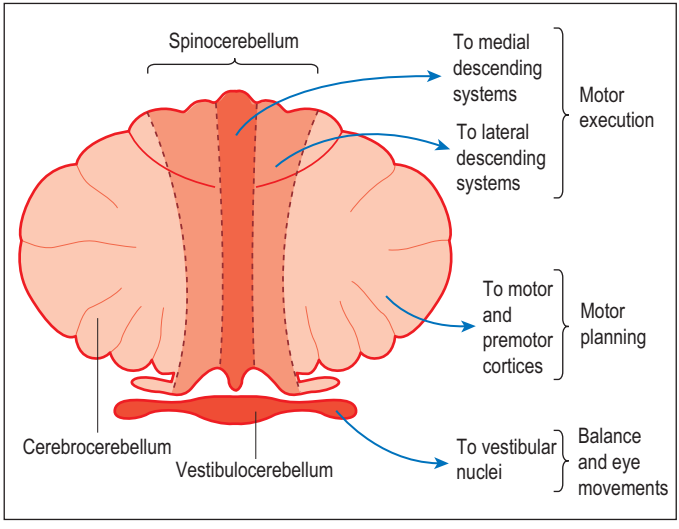


Figure 5.31 Functional anatomy of the cerebellum

Reproduced, with permission, from Barrett KE, Barman SM, Boitano S et al. *Ganong's Review of Medical Physiology*, 23rd edn. Available: http://accessmedicine.com [9 Dec 2010].

Facial muscle weakness (unilateral)

DESCRIPTION

The facial muscles appear asymmetrical due to unilateral weakness.

Facial muscle weakness is characterised by decreased prominence of the facial creases, leading to the characteristic 'facial droop' appearance.[71] There is loss of the forehead furrows (note lower motor neuron pattern), widening of the palpebral fissures with incomplete eye closure (note lower motor neuron pattern), Bell's phenomenon, flattening of the nasolabial fold and limited retraction of the angle of the mouth.[71] Bell's phenomenon is the presence of upward and outward eye deviation during blinking, apparent with incomplete eyelid closure of any cause.

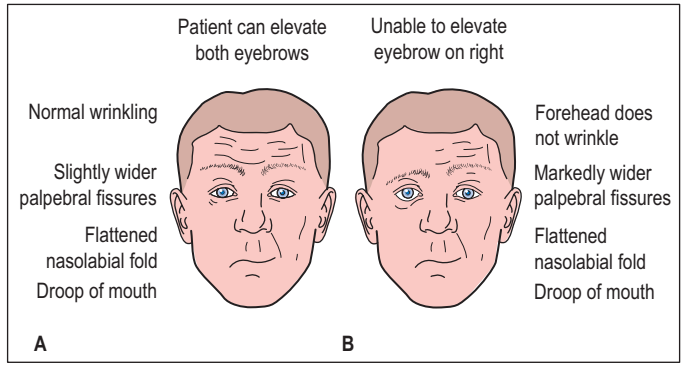


Figure 5.32 Typical appearance of: **A**, upper motor neuron (central) facial weakness; and **B**, lower motor neuron (peripheral) facial weakness

Reproduced, with permission, from Stern TA et al, *Massachusetts General Hospital Comprehensive Clinical Psychiatry*, 1st edn, Elsevier Health Sciences, 2008: Fig 72-7.

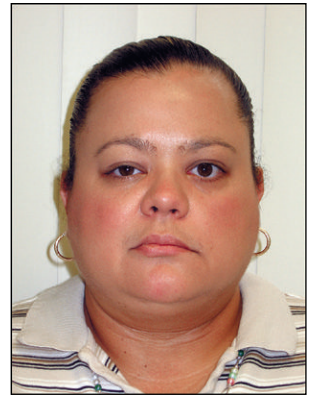


Figure 5.33 Left facial nerve (peripheral) palsy

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 74–9.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[6]

UPPER MOTOR NEURON

- Motor cortex
- ↓
- Corona radiata, subcortical white matter
- ↓
- Posterior limb, internal capsule
- ↓
- Pyramidal tracts, brainstem
- ↓
- ∅ Decussation
- ↓
- ↔ Bilateral supranuclear innervation (upper facial muscles)
- ↓

LOWER MOTOR NEURON

- Facial nerve nuclei pons
- ↓
- Facial nerve fascicle
- ⇒ Abducens nuclei
- ↓
- Facial nerve
- ⇒ Cerebellopontine angle
- ⇒ Internal acoustic meatus
- ↓
- Geniculate ganglion
- ↓
- × Lacrimal gland
- ⇒ Mastoid sinus
- × Stapes
- × Tongue
- × Submandibular glands
- ⇒ Stylomastoid foramen
- × Facial muscles

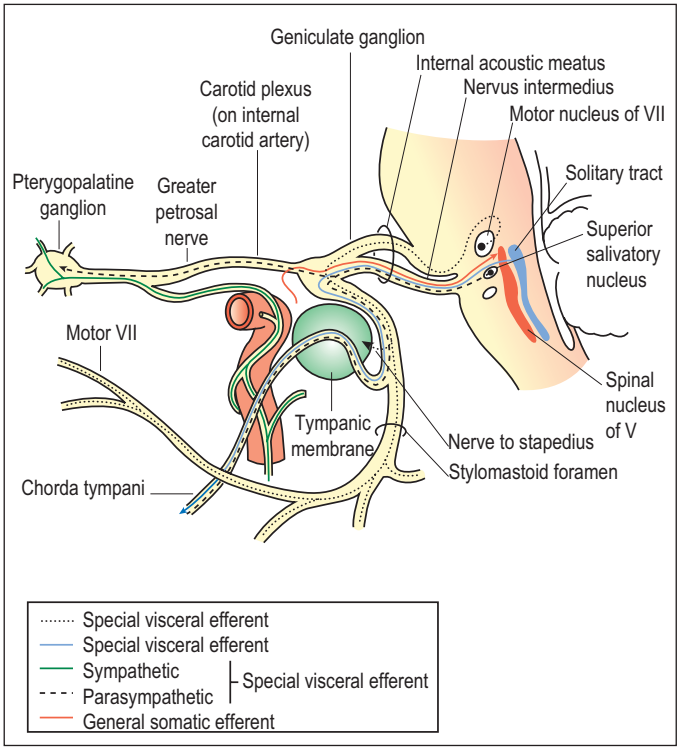


Figure 5.34 Functional anatomy of the facial nerve

Reproduced, with permission, from Dyck PJ, Thomas PK, *Peripheral Neuropathy*, 4th edn, Philadelphia: Saunders, 2005: Fig 50-4.

CONDITION/S ASSOCIATED WITH

Upper motor neuron

COMMON

- MCA territory cerebral infarction
- Cerebral haemorrhage

LESS COMMON

- Lacunar infarction, posterior limb internal capsule
- Mass lesion (e.g. tumour, abscess, AVM)

Lower motor neuron (i.e., facial nerve palsy)[1,6,71,72]

COMMON

- Bell's palsy (idiopathic facial nerve palsy) – 65%[72]
- Trauma – 25%[72]

LESS COMMON

- Tumour (e.g. acoustic schwannoma, cholesteatoma) – 5%[72]
- Diabetic mononeuropathy/ microvascular infarction
- Ramsay Hunt syndrome
- HIV infection
- Lyme disease
- Sarcoidosis

MECHANISM/S

Unilateral facial weakness is caused by:

1. upper motor neuron weakness
2. lower motor neuron weakness (i.e., facial nerve palsy).

UPPER MOTOR NEURON WEAKNESS

Upper motor neuron facial weakness is characterised by weakness, limited to the lower contralateral facial muscles, due to bilateral supranuclear innervation and bilateral upper facial cortical representation in the motor cortex (see Figure 5.35A).[73] Upper motor neuron facial weakness may be associated with arm and/or leg weakness, and dominant or non-dominant cortical localising signs.

Upper motor neuron lesions are also associated with selective weakness of either voluntary facial movements (e.g. patient asked to smile) or involuntary facial movements (e.g. provoked laughter). Cortical predominant lesions are associated with voluntary weakness that is more pronounced than involuntary weakness.[71] Subcortical white matter or internal capsule lesions are associated with emotional facial weakness that may be more pronounced than volitional facial weakness.[71] Lower motor neuron weakness typically affects both equally. The pathways for emotional or involuntary facial muscle function are not known.[71]

LOWER MOTOR NEURON WEAKNESS (I.E., FACIAL NERVE PALSY)

Lower motor neuron facial weakness is characterised by ipsilateral upper and lower facial muscle weakness.[6,71] The facial nerve is the final common pathway of facial

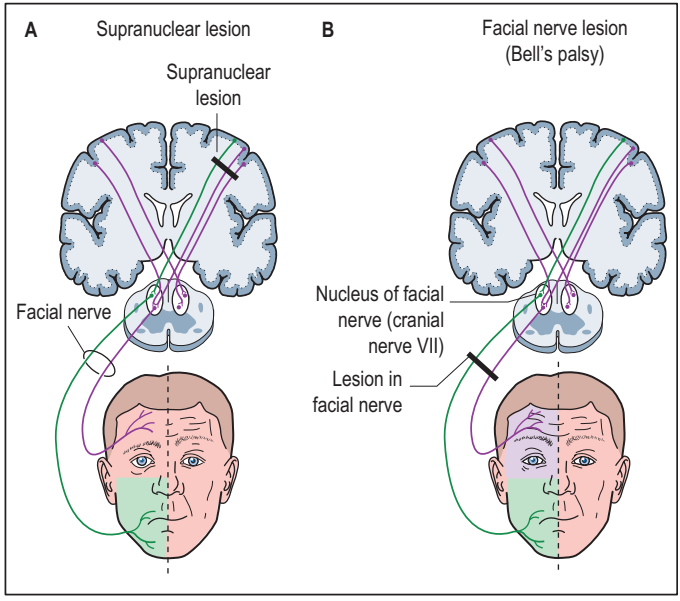


Figure 5.35 Schematic representation of innervation of the facial muscles

A Upper motor neuron (central) weakness results in limited lower facial muscle weakness with sparing of the upper facial muscles. **B** Lower motor neuron (peripheral) weakness results in complete unilateral facial muscle weakness.

Reproduced, with permission, from Timestra JD, Khatkhate N, Am Fam Phys 2007; 76(7): 997–1002.

muscle innervation. Lesions of the peripheral nerve result in complete unilateral facial muscle weakness (see Figure 5.35B). Associated features include hyperacusis, abnormal taste sensation in the anterior two-thirds of the tongue, efferent abnormality of the corneal reflex, a dry irritated eye, abnormal sensation and/or a vesicular eruption in the oropharnx or external auditory meatus (note vesicular eruption in Ramsey Hunt syndrome only). See Table 5.12 for mechanisms of clinical findings in facial nerve palsy.

SIGN VALUE

Unilateral facial muscle weakness should be evaluated rapidly to exclude a central or upper motor neuron lesion, which is most commonly caused by cerebral infarction or cerebral haemorrhage.

The frequencies of causes of lower motor neuron facial weakness are listed in Table 5.13.

TABLE 5.12 Mechanisms of clinical findings in facial nerve palsy

Clinical finding	Mechanism
• Complete facial muscle weakness	→ Facial nerve innervates ipsilateral upper and lower facial muscles
• Hyperacusis	→ Ipsilateral stapedius muscle weakness
• Dysgeusia, anterior two-thirds of tongue	→ Facial nerve supplies ipsilateral anterior two-thirds of tongue
• Dry irritated eye	→ Orbicularis oculi muscle weakness results in incomplete eye closure → Lacrimal gland dysfunction
• Abnormal corneal reflex (efferent)	→ Facial nerve forms efferent limb of the corneal reflex
• Abnormal sensation, oropharynx or external auditory meatus	→ Facial nerve branches innervate ipsilateral oropharynx and external auditory meatus
• Vesicular eruption, oropharynx or external auditory meatus	→ Ramsey Hunt syndrome, or reactivation herpes zoster infection of geniculate ganglion, results in vesicular eruption in distribution of cutaneous nerve branches

TABLE 5.13 Causes of facial nerve (CNVII) palsy[74,75]

Cause	Prevalence
Bell's palsy (idiopathic facial nerve palsy)	50–87%
Surgical or accidental trauma	5–22%
Ramsay Hunt syndrome	7–13%
Tumours (e.g. cholesteatoma or parotid tumours)	1–6%
Miscellaneous	8–11%

Fasciculations

DESCRIPTION

Fasciculations are involuntary, nonrhythmic contractions of small muscle groups caused by spontaneous firing of motor units.[4] They appear on the surface of the muscle as fine, rapid, flickering contractions, irregular in timing and location.[57]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

LOWER MOTOR NEURON

- Anterior horn, spinal cord

↓

- Nerve root

⇒ Intervertebral disc

⇒ Intervertebral foramen

↓

- Nerve plexus (e.g. brachial plexus)

↓

- Peripheral nerve

⇒ Potential sites of nerve entrapment (e.g. carpal tunnel)

↓

→ Neuromuscular junction

↓

× Motor unit, skeletal muscle

CONDITION/S ASSOCIATED WITH[4,57,76]

Common

- Benign fasciculations
- Motor neuron disease (e.g. amyotrophic lateral sclerosis)
- Radiculopathy

Less common

- Depolarising paralytic agent (e.g. succinylcholine)
- Cholinergic toxicity (e.g. organophosphate toxicity)
- Funnel-web spider bite
- Thyrotoxicosis
- Poliomyelitis
- Spinal muscular atrophy

MECHANISM/S

Fasciculations are caused by spontaneous firing of motor units.[57,76] Mechanisms of fasciculations include:

1. benign fasciculations
2. lower motor neuron disorders
3. toxins and drugs.

Benign fasciculations

Fasciculations in the setting of an otherwise normal neurological exam are termed benign fasciculations. Benign fasciculations may be exacerbated by mental or physical fatigue, caffeine, smoking or sympathomimetic agents.[57]

Lower motor neuron disorders

Denervation and reinnervation of muscle fibres secondary to lower motor neuron disease causes the spontaneous excitation of individual motor units.[31] Pathological fasciculations are most common in disorders of the anterior horn cells (e.g. motor neuron disease, poliomyelitis), radiculopathy and, less commonly, in entrapment mononeuropathy and peripheral neuropathy.[77] The distribution of fasciculations (e.g. nerve root, peripheral nerve, hands, tongue) and the presence of lower motor neuron signs (e.g. muscle wasting, hypotonia, weakness, hyporeflexia) are important when considering potential aetiologies. Fasciculations of the tongue are associated with motor neuron disease.

Toxins and drugs

CHOLINERGIC TOXICITY

Cholinergic toxicity (e.g. organophosphate poisoning) causes fasciculations due to potentiation of acetylcholine at the neuromuscular junction. Associated features of the cholinergic toxidrome include diarrhoea, urination, miosis, bradycardia, bronchorrhoea, lacrimation, salivation and sweating.

FUNNEL-WEB SPIDER VENOM

The funnel-web spider produces a toxin that inhibits the inactivation of sodium channels, resulting in neurotransmitter

release and prolonged alpha motor neuron depolarisation, causing spontaneous excitation of skeletal muscle groups.[77]

SIGN VALUE

Fasciculations in the setting of an otherwise normal neurological examination are likely benign fasciculations.[78,79]

Fasciculations in addition to lower motor neuron signs (e.g. hypotonia, weakness, hyporeflexia) are evidence of lower motor neuron dysfunction until proven otherwise. Fasciculations of the tongue occur in approximately one-third of patients with amyotrophic lateral sclerosis.[80]

Gag reflex, absent

DESCRIPTION

Absence of stylopharyngeal muscle and superior pharyngeal muscle constriction following stimulation of the posterior tongue and/or oropharynx.[1] Absence of the gag reflex can be unilateral or bilateral.

CONDITION/S ASSOCIATED WITH[1]

Common

- Normal variant
- Coma
- Drugs (e.g. ethanol, benzodiazepine, opioid)
- Lateral medullary syndrome (Wallenberg's syndrome)

Less common

- Cerebellopontine tumour (e.g. acoustic schwannoma)
- Internal carotid artery dissection
- Glomus tumour

MECHANISM/S

The afferent limb of the gag reflex is mediated by the glossopharyngeal nerve (CNIX), whereas the efferent limb is mediated by the glossopharyngeal nerve (CNIX) and the vagus nerve (CNX).[1] External factors, such as nausea or chronic emesis, may confound the evaluation of the gag reflex, as they may sensitise or desensitise the gag response. Visual,

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[1,81,82]

CENTRAL PATHWAYS

- Vomiting centre, brainstem
- Cortical areas

AFFERENT LIMB – GLOSSOPHARYNGEAL NERVE (CNIX)

⊗ 'Trigger zones' – palatoglossal and palatopharyngeal folds, base of tongue, palate, uvula, posterior pharyngeal wall

↓

- Glossopharyngeal nerve fibres

↓

- Petrosal ganglion

⇒ Jugular foramen

↓

- Solitary nucleus, medulla

↓

EFFERENT LIMB – GLOSSOPHARYNGEAL NERVE (CNIX)

- Nucleus ambiguus, medulla

⇒ Jugular foramen

↓

- Petrosal ganglion

↓

× Stylopharyngeus and superior pharyngeal constrictor muscles

EFFERENT LIMB – VAGUS NERVE (CNX)

- Nucleus ambiguus and dorsal motor nucleus, medulla

↓

- Vagus nerve

⇒ Jugular foramen

⇒ Nodose ganglion

↓

× Palatal constrictors and intrinsic laryngeal muscles

auditory and olfactory stimuli may also sensitise the gag response.[83,84] The gag reflex is absent in a significant percentage of normal individuals.[85] Causes of an absent gag reflex include:

1. normal variant
2. generalised CNS depression
3. glossopharyngeal nerve (CNIX) lesion
4. vagus nerve (CNX) lesion
5. lateral medullary syndrome (Wallenberg's syndrome).

Normal variant

The gag reflex is absent in a significant proportion of the population. Absence of the gag reflex is likely caused by suppression of the reflex by higher cortical centres and/or normal desensitisation of the reflex response with ageing.

Generalised CNS depression

The obtunded or comatose patient may have an absent gag reflex due to generalised central nervous system dysfunction.

Glossopharyngeal nerve lesion

Glossopharyngeal nerve palsy causes ispilateral loss of the gag reflex, decreased pharyngeal elevation, dysarthria and dysphagia.[1] Causes of glossopharygneal nerve dysfunction include cerebellopontine angle tumours, Chiari I malformations, jugular foramen syndrome, neoplasia and iatrogenic injury following laryngoscopy or tonsillectomy.[1]

Vagus nerve lesion

Vagus nerve dysfunction causes ipsilateral loss of pharyngeal and laryngeal sensation, unilateral loss of sensation in the external ear, dysphagia, hoarseness, unilateral paresis of the uvula and soft palate, and deviation of the uvula away from the side of the lesion.[1] Causes of vagus nerve dysfunction include internal carotid artery dissection, neoplasia and trauma.

Lateral medullary syndrome (Wallenberg's syndrome)

Lateral medullary syndrome most commonly results from posterior inferior cerebellar artery (PICA) territory infarction due to vertebral artery insufficiency. Infarction of the solitary nucleus and/or nucleus ambiguus in the medulla may result in an absent ipsilateral gag reflex.

SIGN VALUE

An absent gag reflex occurs in a significant percentage of the normal population. In a study of 140 healthy subjects at various ages, the gag reflex was absent in 37% of subjects, and pharyngeal sensation was absent in only 1 patient.[85]

Gerstmann's syndrome

DESCRIPTION

Gerstmann's syndrome is a disorder of higher visuospatial function.[86] Gerstmann's syndrome is a tetrad:[6]

1. acalculia – difficulty with simple addition and subtraction
2. agraphia – difficulty with writing a sentence
3. left/right confusion – difficulty identifying left- and right-sided body parts
4. finger agnosia – difficulty correctly identifying each finger.

Typically, other deficits coexist (e.g. aphasia, apraxia, amnesia and intellectual impairment).[6]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

- Angular gyrus, dominant parietal lobe

⇒ Subcortical white matter, intraparietal connections[87]

CONDITION/S ASSOCIATED WITH[88]

Common

- MCA territory cerebral infarction
- Cerebral haemorrhage
- Vascular dementia

Less common

- Alzheimer's disease
- Mass lesion (e.g. tumour, abscess, AVM)

MECHANISM/S

Gertsmann's syndrome is typically associated with a lesion in the angular gyrus of the dominant parietal lobe.[86,89] Each component of Gertsmann's syndrome, individually, has poor localising value and can occur with a variety of lesions. It is unclear whether the four components of Gerstmann's syndrome truly share a common neural pathway or whether they cluster together in large, dominant parietal lesions.[86,89] A recent study, using structural and functional neuroimaging in normal subjects, mapped cortical activation patterns of the brain associated with components of Gerstmann's tetrad. Each component of Gerstmann's syndrome was associated with a variety of cortical and subcortical regions. Gerstmann's syndrome likely results from damage to a focal region of subcortical white matter resulting in intraparietal disconnection.[87]

SIGN VALUE

Gerstmann's syndrome is a dominant cortical localising sign.

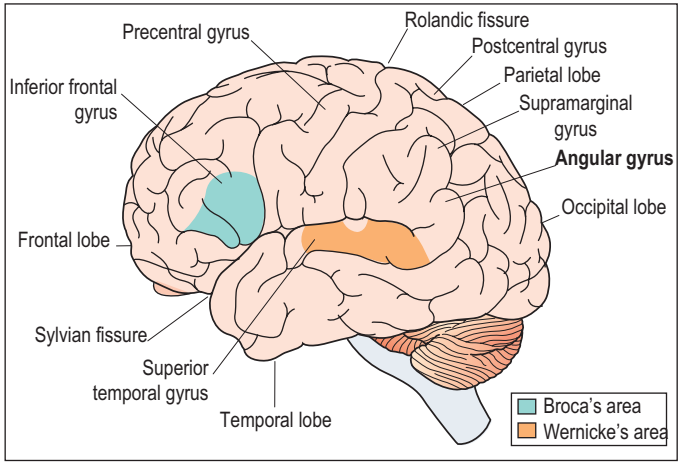


Figure 5.36 Angular gyrus, dominant parietal lobe in Gerstmann's syndrome

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 12A-1.

Glabellar reflex (Myerson's sign)

DESCRIPTION

Tapping the glabella (i.e., between the patient's eyebrows) causes blinking, which typically ceases after several taps. Persistent blinking (i.e., more than 4 or 5 blinks) in response to glabellar tapping is abnormal, and is called Myerson's sign.[4]

RELEVANT NEUROANATOMY AND TOPOGRPAHICAL ANATOMY

- Frontal lobes

Figure 5.37 Glabellar tap

CONDITION/S ASSOCIATED WITH

Common

- Cerebral infarction
- Cerebral haemorrhage
- Parkinson's disease
- Alzheimer's dementia
- Vascular dementia

Less common

- Frontotemporal dementia
- Advanced HIV/AIDS dementia

MECHANISM/S

The mechanism of Myerson's sign is not known. The reflex may reappear later in life due to a frontal lobe disease or normal ageing. The reflex is likely mediated by nonprimary motor cortical areas, which exert an inhibitory control of the spinal reflex.[90] Damage to these areas may result in disinhibition and thus 'release' the reflex.[90] The mechanism of Myerson's sign in Parkinson's disease is not known.

SIGN VALUE

Myerson's sign has been described in normal subjects. The prevalence varies significantly between studies.[91–94]

Myerson's sign is also commonly associated with Parkinson's disease.

Global aphasia

DESCRIPTION

Global aphasia is a disturbance of speech with expressive and receptive components (i.e., a combination of Broca's and Wernicke's aphasia).[46] Speech is nonfluent or non-existent, and comprehension is impaired. Naming, repetition, reading and writing are all affected.[46] See 'Wernicke's aphasia' and 'Broca's aphasia' in this chapter.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

- Broca's area – posterior inferior frontal gyrus, dominant hemisphere
- Wernicke's area – posterior superior temporal gyrus, dominant hemisphere

⇒ Superior and inferior divisions, middle cerebral artery (MCA)

CONDITION/S ASSOCIATED WITH[6,95]

Common

- MCA territory infarction
- Cerebral haemorrhage
- Alzheimer's disease
- Vascular dementia

Less common

- Mass lesion (e.g. tumour, abscess, AVM)
- Primary progressive aphasia

MECHANISM/S

Global aphasia (refer to Table 5.14 for clinical features) is caused by a lesion of the posterior inferior frontal gyrus (i.e., Broca's area), the posterior superior temporal gyrus of the dominant hemisphere (i.e., Wernicke's area) and/or the adjacent subcortical white matter.[46] This region is typically supplied by branches of the middle cerebral artery (MCA). The most common cause is MCA territory cerebral infarction. Most patients will have contralateral motor and sensory findings, and contralateral hemianopia.[46]

SIGN VALUE

Global aphasia is a dominant cortical localising sign and is associated with severe motor and sensory deficits. Patients with global aphasia without hemiparesis are more likely to have a better motor and functional recovery following ischaemic stroke.[96]

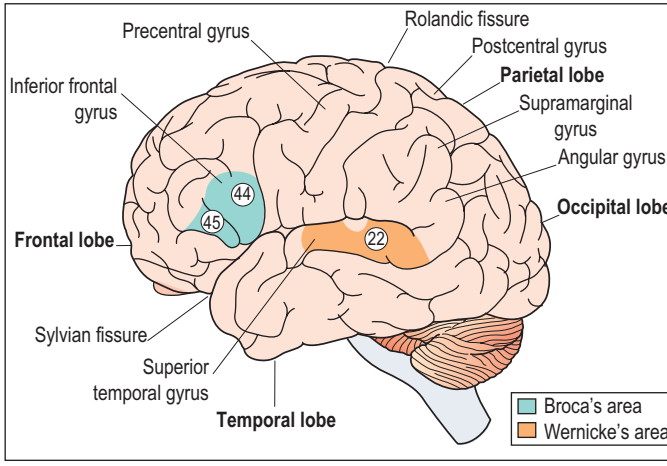


Figure 5.38 Broca's area and Wernicke's area

22 = Brodmann's area 22; 44 = Brodmann's area 44; 45 = Brodmann's area 45.

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 12A-1.

TABLE 5.14 Clinical features of global aphasia

Clinical feature	Abnormality in global aphasia
Spontaneous speech	• Mute or nonfluent
Naming	• Impaired
Comprehension	• Impaired
Repetition	• Impaired
Reading	• Impaired
Writing	• Impaired
Associated signs	• Contralateral motor findings • Contralateral sensory findings • Contralateral hemianopia

Adapted from Kirshner HS, Language and speech disorders: aphasia and aphasiac syndromes. In: Bradley WG, Daroff RB, Fenichel G et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008.

Grasp reflex

DESCRIPTION

The patient involuntary grasps the examiner's fingers, when the examiner strokes the patients' thenar eminence.[4] The grasp reflex is a primitive reflex that is normally present in infancy, which normally disappears in later in life.[4,97]

RELEVANT NEUROANATOMY AND TOPOGRPAHICAL ANATOMY

- Frontal lobes

CONDITION/S ASSOCIATED WITH

Common

- MCA territory cerebral infarction
- Cerebral haemorrhage
- Alzheimer's dementia
- Vascular dementia

Less common

- Frontotemporal dementia
- Parkinson's disease
- Advanced HIV/AIDS

MECHANISM/S

The grasp reflex is present in normal infants from approximately 25 weeks to 6 months of age.[90] The response may be a rudimentary response that was potentially important in arboreal life.[90] The reflex is likely controlled by nonprimary motor cortical areas, which exert an inhibitory control of the spinal reflex following normal central nervous system development.[90] Frontal lobe disease may result in disinhibition of the reflex, and thus 'release' the reflex.

SIGN VALUE

In a study of patients admitted to a neurology service, a positive grasp reflex predicted lesions in the frontal lobe, deep nuclei or subcortical white matter with a sensitivity of 13%, specificity of 99% and a positive likelihood ratio of 20.2.[98]

Hand dominance

DESCRIPTION/MECHANISM/S

Hand dominance, or 'handedness' (e.g. right-handedness, left-handedness, or ambidexterity), is clinically significant in the context of dominant cortical localising signs and/or non-dominant cortical localising signs (see Table 5.15). The side of hand dominance correlates with the side of the dominant cerebral hemisphere and therefore has potential localising value.

- Right hand dominance:
  - 96% of patients have left-sided dominant cerebral hemisphere[99]
  - 4% of patients have right-sided dominant cerebral hemisphere[99]
- Left hand dominance:
  - 73% of patients have left-sided dominant cerebral hemisphere[99]
  - 27% of patients have right-sided dominant cerebral hemisphere[99]

SIGN VALUE

In patients with dominant or non-dominant cortical localising signs, hand dominance has potential localising value.

TABLE 5.15 Dominant and non-dominant cortical localising signs

Dominant cortical localising signs	Non-dominant cortical localising signs
• Aphasia • Gerstmann's syndrome	• Hemineglect syndrome • Anosognosia • Apraxia

Hearing impairment

DESCRIPTION

Hearing is evaluated at the bedside with the whispered voice test (note that this is a poor screening test), Weber test and Rinne test. Clinically, significant hearing loss (i.e., >30 dB) will be missed roughly 50% of the time without formal evaluation (e.g. audiometry).[100]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[18,101,102]

⇒ External ear canal
↓
⇒ Tympanic membrane
↓
⇒ Malleus, incus, stapes bones
↓
⇒ Middle ear
↓
⊗ Cochlea
↓
• Vestibulocochlear nerve (CNVIII)
⇒ Mastoid sinus
⇒ Internal acoustic meatus
⇒ Cerebellopontine angle
↓
• Brainstem nuclei
↓
• Brainstem ascending sensory fibres
↓
• Inferior colliculi
↓
• Medical geniculate nuclei, thalamus
↓
• Auditory cortex, transverse gyri of Heschl, temporal lobe

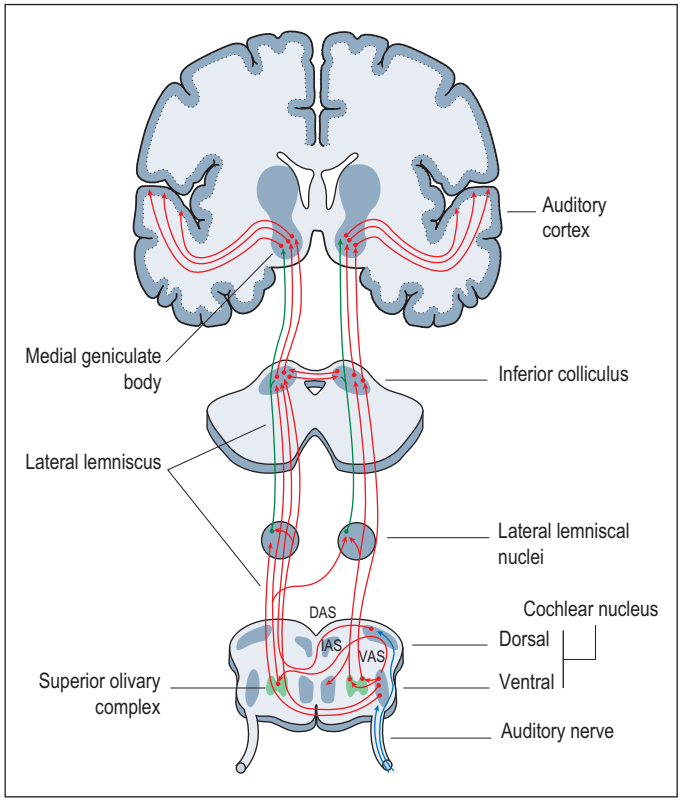


Figure 5.39 Central auditory pathways

DAS = dorsal acoustic stria; IAS = intermediate acoustic stria; VAS = ventral acoustic stria.

Reproduced, with permission, from Flint PW et al, *Cummings Otolaryngology: Head and Neck Surgery*, 5th edn, Mosby, 2010: Fig 128-6.

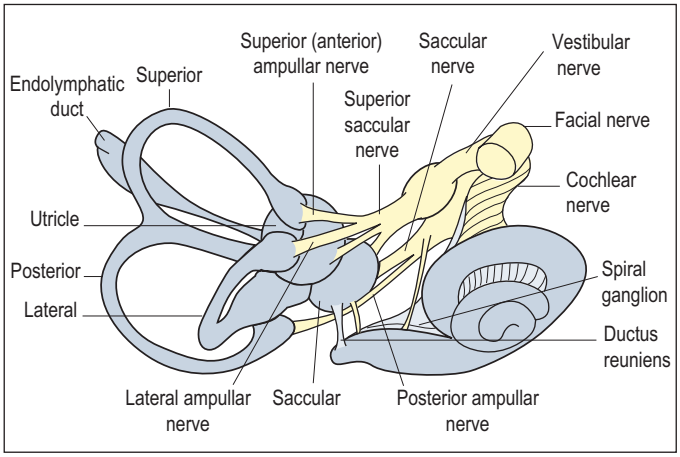


Figure 5.40 The vestibular system and peripheral auditory components

Reproduced, with permission, from Flint PW et al, *Cummings Otolaryngology: Head and Neck Surgery*, 5th edn. Mosby, 2010: Fig 163-1.

CONDITION/S ASSOCIATED WITH[101,102]

Common

- Impacted cerumen
- Presbyacusis (i.e., age-related hearing loss)
- Otitis media with effusion
- Tympanic membrane perforation
- Otosclerosis
- Drugs (e.g. gentamicin, furosemide, aspirin)

Less common

- Ménière's disease
- Vestibular neuritis
- Acoustic schwannoma
- Meningitis
- Cholesteatoma

MECHANISM/S

Mechanisms of hearing loss include:

1. conductive hearing loss
2. sensorineural hearing loss
3. central hearing loss (rare).

Conductive hearing loss

In conductive hearing loss, sound waves are not transmitted to the sensorineural structures of the auditory system. Conductive hearing loss can result from a disorder of the external ear canal, tympanic membrane, ossicles or middle ear.[101,102] The most common cause of conductive hearing loss is cerumen or 'wax' impaction in the external canal.[102] Causes include otitis media with effusion, tympanic membrane perforation, otosclerosis and cholesteatoma.

Sensorineural hearing loss

Sensorineural hearing loss results from dysfunction of the cochlea, the auditory division of the acoustic nerve and/or the vestibulocochlear nerve.[101] Different frequencies of sound are detected in different segments of the spiral-shaped cochlea. In cochlear lesions, hearing levels for varying frequencies are typically unequal.[101] Causes include Ménière's disease, cerebellopontine angle tumours (e.g. acoustic schwannoma), vestibular neuritis and ototoxic drugs (e.g. gentamicin, furosemide, aspirin).

Central hearing loss (rare)

Due to the decussation of sensory fibres above the entry point in the brainstem, the most likely central lesion resulting in unilateral hearing loss is the entry point of the vestibulocochlear nerve fascicles at the pontomedullary junction.[101] Bilateral sensorineural hearing loss may result from bilateral lesions of the primary auditory cortex in the transverse gyri of Heschl.[101]

SIGN VALUE

Asymmetrical sensorineural hearing loss is concerning for a focal neurological lesion (e.g. a tumour in the internal auditory meatus or cerebellopontine area).[101] In a study of patients with >15 dB hearing loss in two or more frequencies, or ≥15% asymmetry in speech discrimination scores, approximately 10% of patients had an identifiable tumour on MRI.[103]

Hemineglect syndrome

DESCRIPTION

Hemineglect syndrome is a disorder of conscious perception, characterised by a lack of awareness of the contralateral visual hemispace and contralateral body (refer to Table 5.16 for clinical features).[6] The patient may be completely unaware of their own body or objects in the neglected space (i.e., anosognosia). The presence of hemineglect is typically evaluated with clock face drawing, search/cancellation and/or line bisection tests.[104]

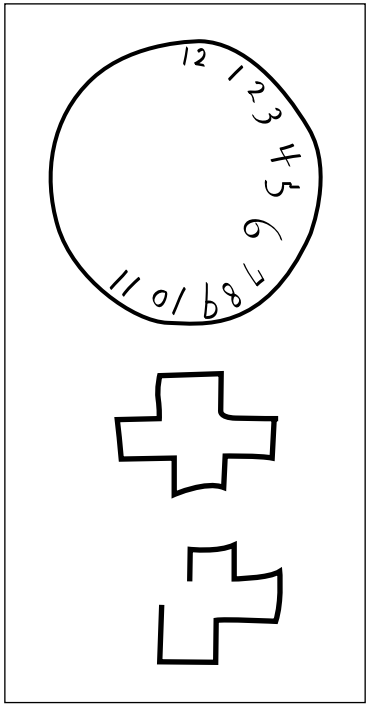


Figure 5.41 Results of clock face drawing in hemineglect syndrome

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 6-3.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

- Temporo-parietal junction, non-dominant hemisphere

CONDITION/S ASSOCIATED WITH

Common

- Non-dominant cerebral infarction
- Non-dominant cerebral haemorrhage

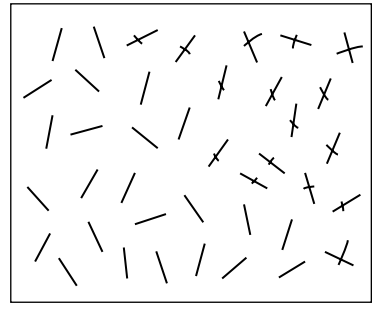


Figure 5.42 Results of search/cancellation task in hemineglect syndrome

Based on Medscape, Spatial neglect. Available: http://emedicine.medscape.com/article/1136474-media [5 Apr 2011].

TABLE 5.16 Clinical features of hemineglect syndrome[6,104]

Clinical feature	Characteristics
Sensory neglect	• Patient ignores visual, tactile or auditory stimuli in the contralateral hemispace
Motor neglect	• Patient performs fewer movements in the contralateral hemispace
Combined sensory/motor neglect	• Combination of the features above
Conceptual neglect	• Patient's internal representation of own body and/or external environment exhibits neglect

Less common

- Non-dominant mass lesion (e.g. tumour, abscess, AVM)

MECHANISM/S

The most common cause of hemineglect syndrome is a lesion at the temporo-parietal junction of the non-dominant hemisphere.[105,106] These areas of the brain mediate conscious representation of sensation, motor activities such as visual scanning and limb exploration, and motivational relevance.[107] The exact location responsible for hemineglect syndrome is unclear. Several areas have been implicated and include: the angular gyrus of the posterior parietal cortex in the right hemisphere, right superior temporal cortex, right inferior parietal lobule, cingulate gyrus, thalamus and basal ganglia.[108]

SIGN VALUE

Hemineglect syndrome is a non-dominant cortical localising sign. In a study of 140 consecutive patients admitted with right hemisphere stroke, visual hemineglect syndrome was present in 56% of patients.[109]

High stepping gait (steppage gait)

DESCRIPTION

A high stepping gait (i.e., steppage gait) is characterised by pronounced hip and knee flexion, in order to clear the lower limb or limb(s) with foot drop during leg swing.[43,28]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

- Nerve root (L5)

⇒ Intervertebral disc

⇒ Intervertebral foramina

↓

- Peripheral nerve (sciatic nerve, common peroneal nerve)

⇒ Potential sites of nerve injury (e.g. trauma, head of fibula)

↓

× Muscles of the anterior compartment, leg

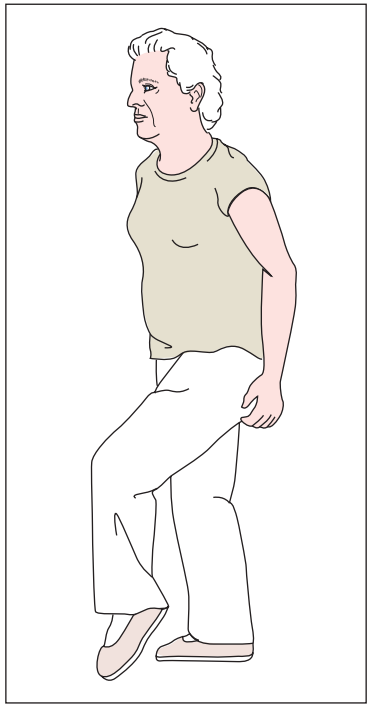


Figure 5.43 High stepping gait

Based on Neurocenter. Available: http://neurocenter.gr/N-S.html [5 Apr 2011].

CONDITION/S ASSOCIATED WITH[3]

Common

- Common peroneal nerve compression mononeuropathy
- L5 radiculopathy
- Length-dependent peripheral neuropathy (e.g. alcohol, diabetes mellitus)

Less common

- Sciatic nerve palsy
- Hereditary peripheral neuropathy (e.g. Marie–Charcot–Tooth disease)
- Myopathy (e.g. scapuloperoneal muscular dystrophy)

MECHANISM/S

High stepping gait is associated with foot drop. Foot drop is caused by weakness of the anterior compartment muscles of the leg (e.g. tibialis anterior, extensor hallicus longus, extensor hallicus brevis muscles). Causes of high stepping gait include:

1. L5 radiculopathy
2. common peroneal nerve palsy
3. sciatic nerve palsy
4. length-dependent peripheral neuropathy
5. Charcot–Marie–Tooth disease
6. scapuloperoneal muscular dystrophy.

L5 radiculopathy

The L5 nerve root nerve fibres supply the muscles of the anterior compartment of the leg. The most common causes of L5 radiculopathy are intervertebral disc or intervertebral foramen disease (e.g. osteoarthritis). Other causes of radiculopathy include neoplasia, epidural abscess and trauma. Associated features of L5 radiculopathy include ankle dorsiflexor weakness and sensory abnormalities (e.g. pain, sensory loss) in the L5 dermatome (i.e., lateral aspect of the foot).

Common peroneal nerve palsy

The common peroneal nerve branches into the deep and superficial peroneal nerves, which innervate the muscles of the anterior and lateral compartments of the leg, respectively. The common peroneal nerve is vulnerable to traumatic injury due to its superficial location adjacent to the fibular head (see Figure 5.44). Common causes of peroneal nerve palsy include penetrating or

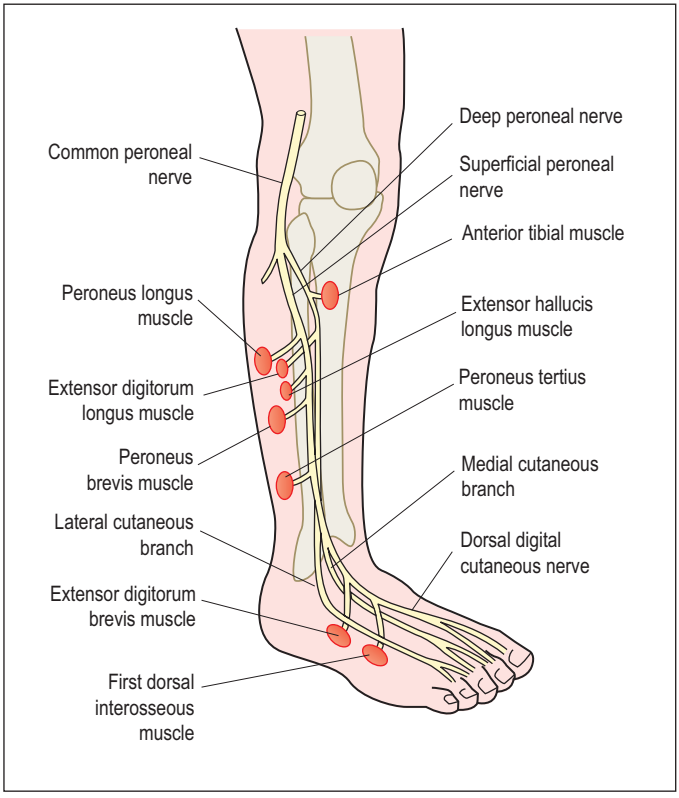


Figure 5.44 Anatomy of the common, superficial and deep peroneal (fibular) nerves

Reproduced, with permission, from Canale ST, Beaty JH, *Campbell's Operative Orthopaedics*, 11th edn, St Louis: Mosby, 2007: Fig 59-39.

blunt trauma at the fibular head and chronic compression secondary to immobility. Associated features include ankle dorsiflexion weakness (i.e., anterior compartment muscle weakness), ankle eversion weakness (i.e., lateral compartment muscle weakness) and sensory loss of lateral aspect of the leg (due to dysfunction lateral sural cutaneous nerve).

Sciatic nerve palsy

Sciatic nerve palsy results in evidence of common peroneal nerve dysfunction (e.g. dorsiflexion weakness, ankle eversion weakness) and tibial nerve dysfunction (e.g. plantarflexion weakness, decreased/absent ankle jerk reflex). The most common causes are hip fracture–dislocation and penetrating injury of the buttock.[3]

Length-dependent peripheral neuropathy

Causes of length-dependent peripheral neuropathy include diabetes mellitus, alcohol and inherited neuropathies.[3] A wide range of metabolic abnormalities in the peripheral nerve result in axonal degeneration, which starts in the most distal portion of the nerve and progressively affects more proximal fibres.[3] Associated features include a progressive glove-and-stocking pattern of motor deficits and sensory deficits, distal muscle weakness, muscle atrophy, trophic changes and loss of ankle reflexes.[3]

Charcot–Marie–Tooth disease

Charcot–Marie–Tooth (CMT) disease is a form of hereditary motor and sensory neuropathy that results in bilateral peroneal muscular atrophy.[3] Charcot–Marie–Tooth disease is the most common inherited neuropathy.

Scapuloperoneal muscular dystrophy

Scapuloperoneal muscular dystrophy is a rare primary disorder of muscle that affects the anterior compartment muscles.

SIGN VALUE

High stepping gait is associated with foot drop.

Hoarseness

DESCRIPTION

Hoarseness is caused by asynchronous contraction and opposition of the vocal cords.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

UPPER MOTOR NEURON

↔ Bilateral upper motor neuron

LOWER MOTOR NEURON

• Nucleus ambiguus medulla

↓

• Vagus nerve (CNX)

⇒ Jugular foramen

↓

• Right recurrent laryngeal nerve	• Left recurrent laryngeal nerve
⇒ Thoracic cavity	⇒ Thoracic cavity
	⇒ Arch aorta
	⇒ Left atria
↓	↓
× Vocal cord muscles	× Vocal cord muscles

CONDITION/S ASSOCIATED WITH

Common

- Viral laryngitis
- Iatrogenic (e.g. prolonged or traumatic intubation)
- Recurrent laryngeal nerve palsy (e.g. iatrogenic injury)

Less common

- Vocal cord polyps
- Recurrent laryngeal nerve palsy (e.g. Pancoast's tumour, thoracic aortic aneurysm)
- Lateral medullary syndrome (i.e., Wallenberg's syndrome)
- Ortner's syndrome

MECHANISM/S

Hoarseness is caused by:

1. recurrent laryngeal nerve palsy
2. nucleus ambiguus lesion (e.g. lateral medullary syndrome)
3. local disorders of the vocal cords
4. disorders of the cricoarytenoid joint
5. bilateral upper neuron lesions (rare).

Recurrent laryngeal nerve palsy

The recurrent laryngeal nerve, a branch of the vagus nerve, undertakes a long, convoluted course after exiting the medulla, going through the neck and thoracic cavity, under and around the aortic arch (left recurrent laryngeal nerve only), past the left atrium and then up along the trachea to the muscles of the vocal cords. It is susceptible to a diverse variety of insults along the way. Causes include Pancoast's tumour, atrial enlargement (i.e., Ortner's syndrome), thoracic aortic aneurysm and iatrogenic injury following thyroidectomy.[110,111]

Nucleus ambiguus lesion (e.g. lateral medullary syndrome)

Damage to the nucleus ambiguus in the medulla can cause hoarseness. This can be caused by posterior inferior cerebellar artery (PICA) territory infarction in lateral medullary syndrome (see 'Wallenberg's syndrome' in this chapter).

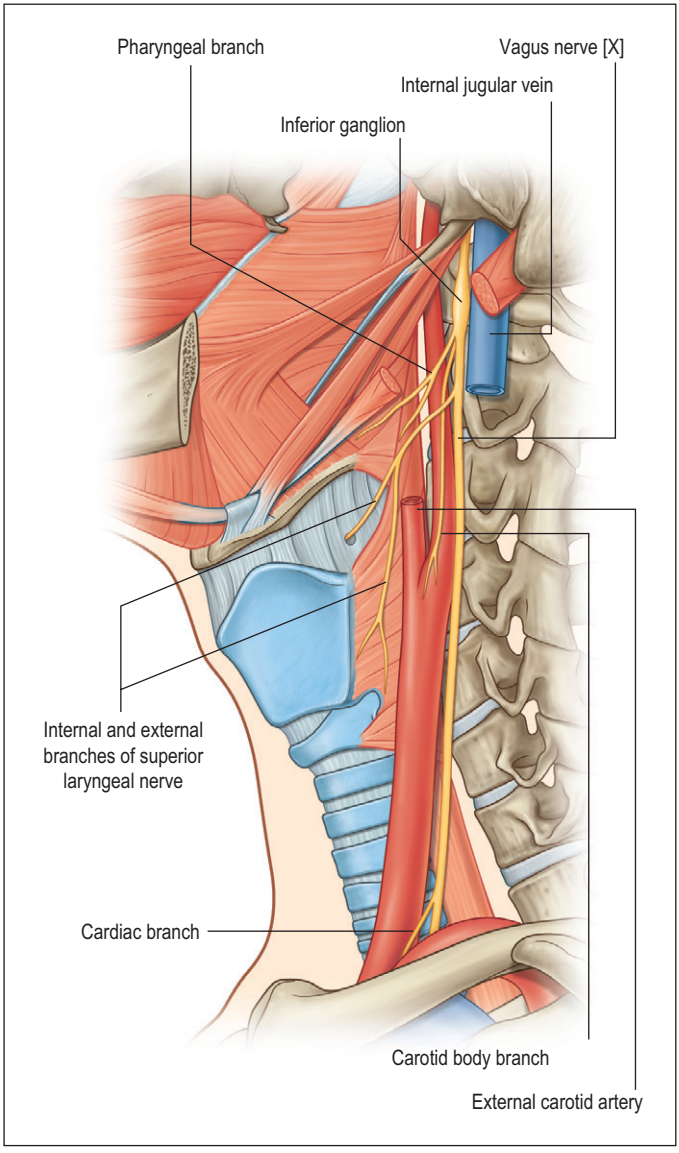


Figure 5.45 Anatomy of the vagus nerve

Reproduced, with permission, from Drake R, Vogl AW, Mitchell AWM, *Gray's Anatomy for Students*, 2nd edn, Philadelphia: Churchill Livingstone, 2009: Fig 8-164.

Local disorders of the vocal cords

Local vocal cord swelling or a mass lesion causing poor vocal cord opposition can lead to asynchronous vibratory contractions of the vocal cords. The most common cause is viral laryngitis. Other causes include vocal cord polyps, tumours (e.g. squamous cell carcinoma) and iatrogenic trauma (e.g. endotracheal intubation).

Disorders of the cricoarytenoid joint[112,113]

Rheumatoid arthritis affecting the cricoarytenoid joint (a synovial joint) may impair the coordinated movement of the vocal cords, resulting in hoarseness.

Bilateral upper motor neuron lesions (rare)

Bilateral upper motor neuron lesions may cause hoarseness, although there are typically severe motor deficits. Unilateral upper motor neuron lesions generally do not cause hoarseness because the nucleus ambiguus receives bilateral cortical innervation.[4]

SIGN VALUE

Hoarseness is most commonly associated with viral laryngitis but can be an important sign of neurological disease. Hoarseness should be interpreted in the context of the overall clinical findings. Isolated hoarseness that lasts longer than 2 weeks is unlikely to be caused by viral laryngitis and should prompt further evaluation.[70]

Hoffman's sign

DESCRIPTION

Sudden stretch of the finger flexors causes involuntary finger flexor contraction due to activation of a monosynaptic stretch reflex.[4]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

UPPER MOTOR NEURON

- Motor cortex

↓

- Corona radiata, subcortical white matter

↓

- Posterior limb, internal capsule

↓

- Pyramidal tracts, medial brainstem

↓

∅ Pyramidal decussation, medulla

↓

- Lateral corticospinal tracts, spinal cord

↓

MONOSYNAPTIC STRETCH REFLEX

→ Inhibitory interneuron
→ Alpha motor neuron
→ Sensory afferent

CONDITION/S ASSOCIATED WITH

Common

- Normal variant
- MCA territory cerebral infarction
- Cerebral haemorrhage
- Lacunar infarction, posterior limb internal capsule

Less common

- Multiple sclerosis
- Spinal cord injury
- Brainstem lesion (i.e., medial medullary syndrome)
- Mass lesion (e.g. tumour, abscess, AVM)

MECHANISM/S

Hoffman's sign is caused by activation of a monosynaptic stretch reflex. Exaggeration of the reflex is caused by hyperreflexia in the setting of upper motor neuron dysfunction (see also 'Hyperreflexia' in this chapter).[57]

SIGN VALUE

Hoffman's sign is a sign of hyperreflexia. It may be present in normal individuals.

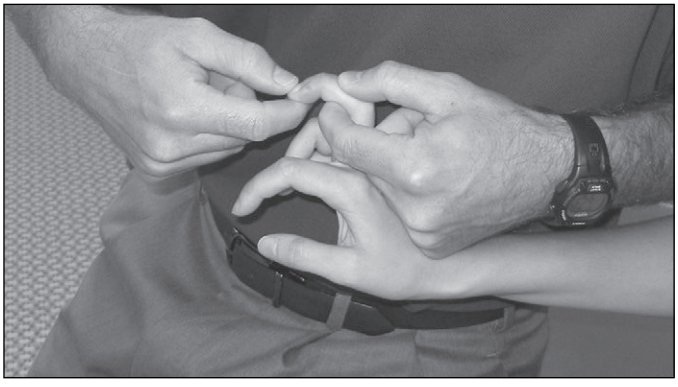


Figure 5.46 Hoffman's sign

Reproduced, with permission, from Fernandez-de-las-Penas C, Cleland J, Huijbregts P (eds), *Neck and Arm Pain Syndromes*, 1st edn, London: Churchill Livingstone, 2011: Fig 9-1.

Horner's syndrome

DESCRIPTION

Horner's syndrome is a triad of unilateral:[4,10,11]

1. miosis
2. ptosis with apparent enophthalmos
3. anhydrosis.

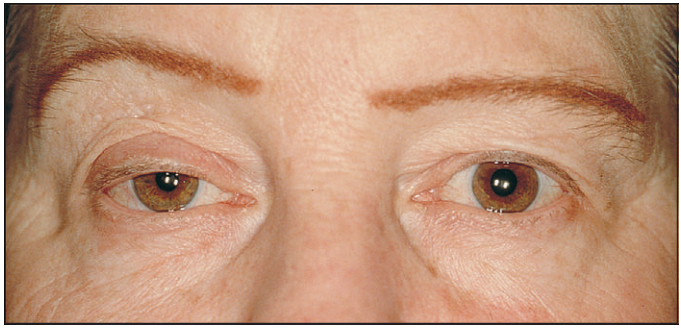


Figure 5.47 Right Horner's syndrome

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 12-5-4.

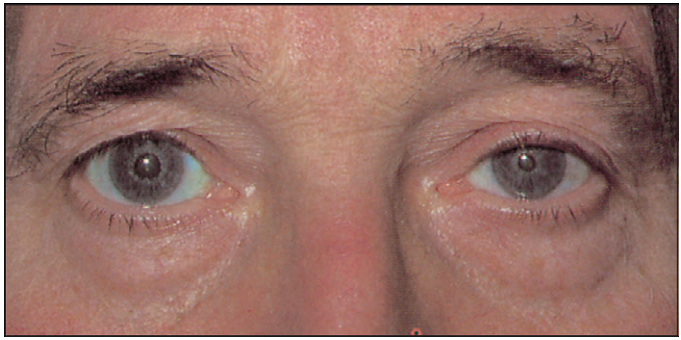


Figure 5.48 Left Horner's syndrome in a patient with syringomyelia

Reproduced, with permission, from Goldman L, Ausiello D, *Cecil Medicine*, 23rd edn, Philadelphia: Saunders, 2007: Fig 450-5.

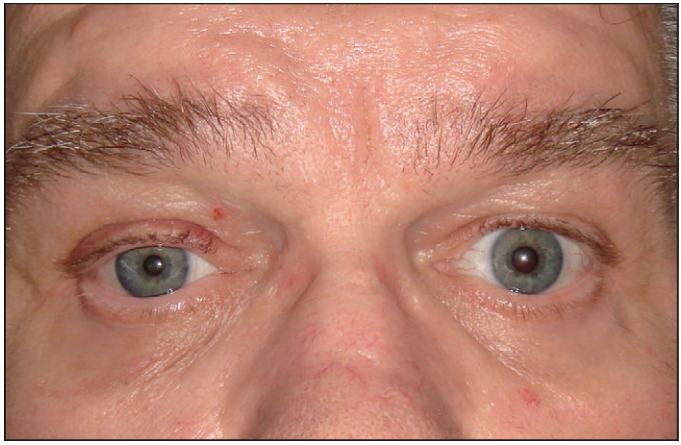


Figure 5.49 Right Horner's syndrome following right neck dissection

Reproduced, with permission, from Flint PW, Haughey BH, Lund VJ et al, *Cummings Otolaryngology: Head & Neck Surgery*, 5th edn, Philadelphia: Mosby, 2010: Fig 122-8.

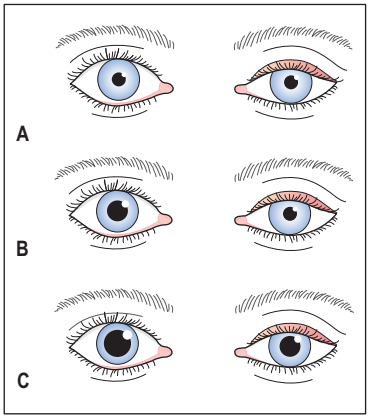


Figure 5.50 Left Horner's syndrome

A Mild upper lid ptosis and miosis in room light. **B** Anisocoria is increased at 5 seconds after the lights are dimmed due to dilation lag of the left pupil. **C** Fifteen seconds after the lights are dimmed, the left pupil exhibits increased dilation compared to the image in **B**.

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 17-6.

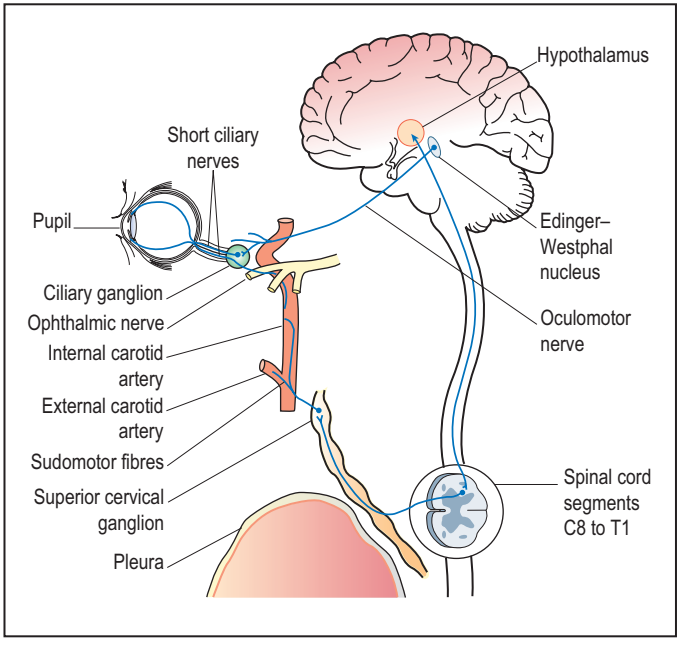


Figure 5.51 Sympathetic and parasympathetic innervation of the pupil

Reproduced, with permission, from Duong DK, Leo MM, Mitchell EL, Emerg Med Clin N Am 2008; 26: 137–180, Fig 3.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

Sympathetic pathway

FIRST-ORDER NEURON
- Hypothalamus

↓
- Sympathetic fibres, brainstem

↓
- Sympathetic fibres, intermediate horn, spinal cord

↓

SECOND-ORDER NEURON (PREGANGLIONIC FIBRE)
- Sympathetic trunk

⇒ Lung apex

↓
- Superior cervical ganglion C2

↓

THIRD-ORDER NEURON (POSTGANGLIONIC FIBRE)
- Superior cervical ganglion C2

⇒ Carotid sheath

⇒ Carotid artery

⇒ Superior orbital fissure

⇒ Cavernous sinus

⇒ Orbital apex

↓
- Ciliary body

↓

× Pupillary dilator muscles

× Superior tarsal muscle

× Sweat glands

CONDITION/S ASSOCIATED WITH[4,10–12]

Common

- Lateral medullary syndrome (Wallenberg's syndrome)
- Pancoast's tumour
- Idiopathic
- Iatrogenic (e.g. complication of carotid endarterectomy)

Less common

- Spinal cord lesion above T1
- Thoracic aortic aneurysm
- Carotid artery dissection
- Complicated migraine
- Cavernous sinus syndrome
- Syringomyelia

MECHANISM/S

Causes of Horner's syndrome are divided into:

1. first-order sympathetic neuron lesion
2. second-order sympathetic neuron lesion
3. third-order sympathetic neuron lesion.

First-order sympathetic neuron lesion

The first-order sympathetic neuron travels from the hypothalamus to the C8–T1 level of the spinal cord. Causes of lesions in the the first-order sympathetic neuron include hypothalamic lesions (e.g., infarct, tumour), lateral medullary syndrome (Wallenberg's syndrome) and syringomyelia.[8,114]

Second-order sympathetic neuron lesion

The second-order sympathetic neuron travels a long intrathoracic course from the C8–T1 level of the spinal cord to the superior cervical ganglion at the level of C2. Associated findings in second-order causes of Horner's syndrome include C8 or T1 nerve roots signs or significant findings in the chest.[8,114] Causes of lesions in the second-order sympathetic neuron include thoracic aortic aneurysm, lower brachial plexus injury (e.g. Klumpke's palsy), Pancoast's tumour, carotid artery dissection and iatrogenic injury following carotid endarterectomy.

Third-order sympathetic neuron lesion

The third-order sympathetic neuron travels from the cervical ganglion at the level of C2 to the pupillary dilator muscle and the superior tarsal muscle. Causes include complicated migraine, head and neck trauma, cavernous sinus syndrome and local eye pathology.[4,10,11]

SIGN VALUE

In the hospital setting, causes of Horner's syndrome vary depending on the admitting service. On a neurology service, 70% of patients with Horner's syndrome have lesions in the first-order neuron (e.g. brainstem stroke is the most common cause).[4,115] On a medicine service, 70% of patients have a lesion of the second-order neuron caused by tumours (e.g. lung and thyroid malignancies) or trauma (e.g. trauma of the neck, chest, spinal nerves, subclavian or carotid arteries).[4,116] On an ophthalmology service, patients are more likely to have second- or third-order neuron lesions (e.g. complicated migraine, skull fracture or cavernous sinus syndrome).[4,10–12]

Hutchinson's pupil

DESCRIPTION

Hutchinson's pupil is a non-reactive dilated pupil caused by oculomotor nerve compression secondary to uncal herniation. Other signs of oculomotor nerve palsy (e.g. extraocular muscle weakness, ptosis) may also be present (see also 'Oculomotor nerve palsy' in this chapter).

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

Pupillary constriction/parasympathetic pathway

EFFERENT LIMB

- Edinger–Westphal nucleus midbrain

↓

- Oculomotor nerve (CNIII)

⇒ Uncus, medial temporal lobe

↓

- Ciliary ganglion

↓

- Short ciliary nerves

↓

× Pupillary constrictor muscles
× Levator palpebrae muscle
× Iris

CONDITION/S ASSOCIATED WITH

- Uncal herniation
  - Intracerebral haemorrhage
  - Epidural haemorrhage
  - Mass lesion (e.g. tumour, abscess, AVM)

MECHANISM/S

Uncal herniation most commonly results from an expanding extra-axial intracranial haematoma or mass.[117] Increasing intracranial volume and intracranial pressure result in cerebral herniation when the expanding intracranial contents (e.g. a mass) exceed the capacity of the cerebral tissue and intracranial contents to accommodate such a change.[117] Cerebral tissue moves in the direction of the pressure gradient (i.e., caudally towards the foramen magnum). Herniation of the medial temporal lobe and uncus may result in compression of the midbrain and oculomotor nerve, resulting in a non-reactive dilated pupil.[6,9,117] See 'Oculomotor nerve palsy' in this chapter.

SIGN VALUE

Hutchinson's pupil is a catatrophic sign of oculomotor nerve compression due to uncal herniation. When present, mortality approaches 100% without prompt medical intervention and surgical decompression.[117]

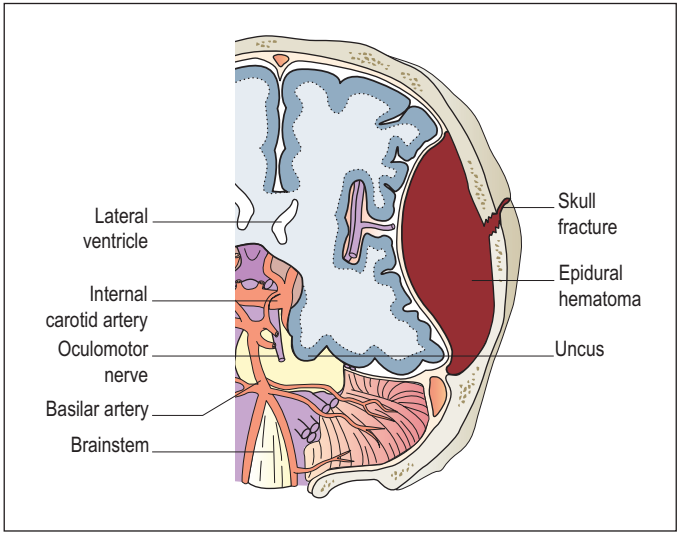


Figure 5.52 Schematic representation of uncal herniation caused by an epidural hematoma, resulting in oculomotor nerve (CNIII) compression

Reproduced, with permission, from Marx JA, Hockberger RS, Walls RM et al, *Rosen's Emergency Medicine*, 7th edn, Philadelphia: Mosby, 2010: Fig 38-5.

Hutchinson's sign

DESCRIPTION

Hutchinson's sign is a vesicular eruption on the tip of the nose due to a reactivation of herpes zoster (VZV) infection involving the nasociliary nerve, a branch of the ophthalmic division of the trigeminal nerve (CNV V1).

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

⊗ Sensory receptors light touch/pain/temperature

↓

• Ophthalmic division (V1) trigeminal nerve (CNV)

⇒ Cavernous sinus

⇒ Superior orbital fissure

↓

• Trigeminal (Gasserian) ganglion, Meckel's cave petrous bone

CONDITION/S ASSOCIATED WITH[1]

Common

- Varicella zoster virus (VZV) reactivation (i.e., 'shingles')

MECHANISM/S

Herpes zoster reactivation involving the nasociliary branch of the ophthalmic division of the trigeminal nerve typically pre-empts ocular involvement (i.e., herpes zoster ophthalmicus).

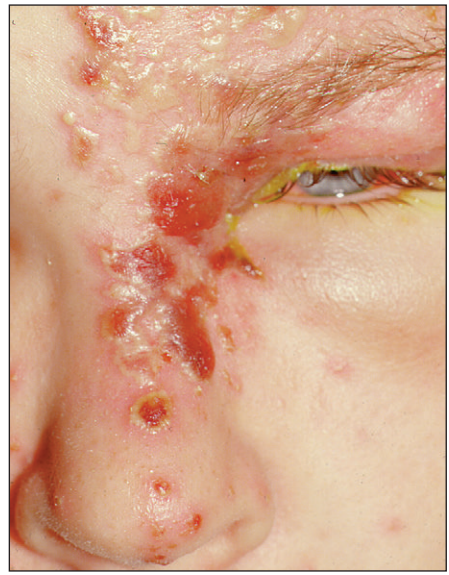


Figure 5.53 Hutchinson's sign

Herpes zoster reactivation involving the nasociliary nerve

Reproduced, with permission, from Palay D, Krachmer J, *Primary Care Ophthalmology*, 2nd edn, Philadelphia: Mosby, 2005: Fig 6-9.

SIGN VALUE

Early identification of Hutchinson's sign strongly predicts eye involvement (i.e., herpes zoster ophthalmicus).[118]

Hyperreflexia

DESCRIPTION

Stretch reflexes are more brisk than normal. Hyperreflexia is an upper motor neuron sign. Hyperreflexia is significant in the following clinical scenarios:[4]

1. hyperreflexia PLUS upper motor neuron signs (e.g. spasticity, weakness, clonus, Babinski sign)
2. reflex amplitude is asymmetric
3. reflex is brisk compared to reflexes from a higher spinal level, signifying potential spinal cord disease.

The National Institute of Neurological Disorders and Stroke (NINDS) describes a standardised method of grading reflexes (see Table 5.17).[4]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

UPPER MOTOR NEURON
- Motor cortex
- ↓
- Corona radiata, subcortical white matter
- ↓
- Posterior limb, internal capsule
- ↓
- Corticospinal tracts, medial brainstem
- ↓
- ∅ Pyramidal decussation, medulla
- ↓
- Lateral corticospinal tracts, spinal cord
- ↓

MONOSYNAPTIC STRETCH REFLEX
- → Inhibitory interneuron
- → Alpha motor neuron
- → Sensory afferent

CONDITION/S ASSOCIATED WITH

Common

- Cerebral infarction
- Cerebral haemorrhage
- Lacunar infarction, posterior limb internal capsule

Less common

- Multiple sclerosis
- Spinal cord injury
- Mass lesion (e.g. tumour, abscess, AVM)

MECHANISM/S

Upper motor neuron lesions cause an increase in gamma motor neuron activity and a decrease in inhibitory interneuron activity, resulting in a state of hyperexcitability of alpha motor neurons.[119] Associated findings in upper motor neuron disease include spasticity, weakness, pronator drift, Babinski sign and hyperreflexia. Upper motor neuron lesions cause contralateral hyperreflexia if present above the pyramidal decussation (e.g. pons, medulla, posterior limb internal capsule, motor cortex) and ipsilateral hyperreflexia

TABLE 5.17 NINDS Muscle Stretch Reflex Scale[57]

Grade	Findings
0	Reflex absent
1	Reflex small, less than normal
	Includes a trace response or a response brought out only by reinforcement
2	Reflex in lower half of normal range
3	Reflex in upper half of normal range
4	Reflex enhanced, more than normal
	Includes clonus if present, which optionally can be noted in an added verbal description of the reflex

Adapted from McGee S, *Evidence Based Physical Diagnosis*, 2nd edn, St. Louis: Saunders, 2007.

if the lesion is present below the pyramidal decussation (e.g. spinal cord). The distribution of hyperreflexia and associated upper motor neuron signs is important when considering a potential aetiology (see Tables 5.16, 5.18, 5.19).

SIGN VALUE

Hyperreflexia is an upper motor neuron sign.

Refer to Table 5.18 for clinical utility.

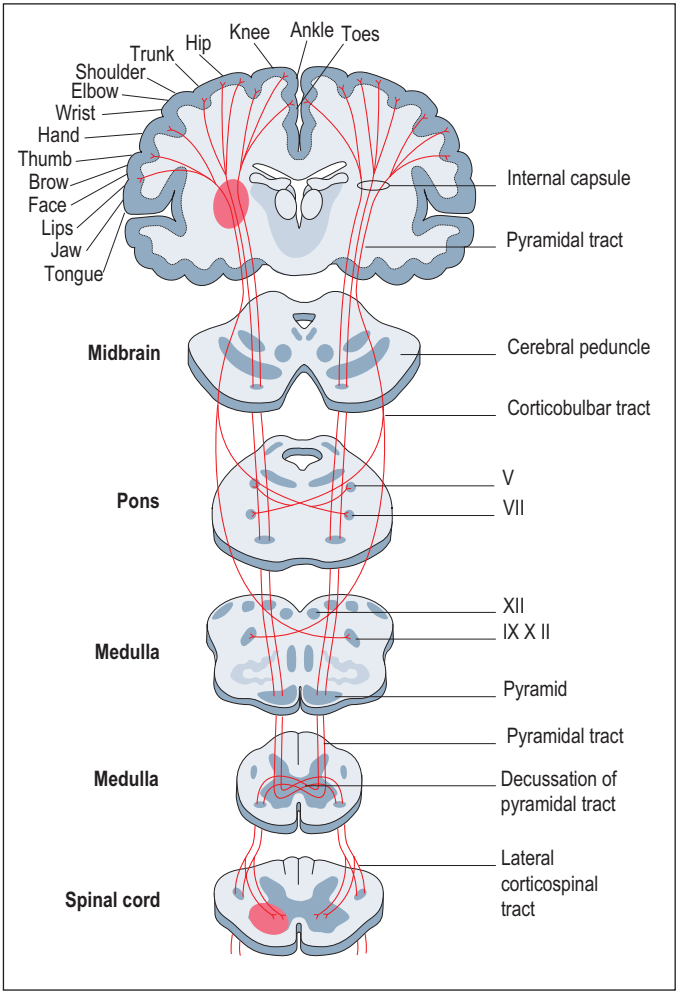


Figure 5.54 Upper motor neuron anatomy

Reproduced, with permission, from Clark RG, *Manter and Gatz's Essential Neuroanatomy and Neurophysiology*, 5th edn, Philadelphia: FA Davis Co, 1975.

TABLE 5.18 Clinical utility of hyperreflexia in unilateral hemisphere lesions[57]

	Sensitivity	Specificity	Positive LR	Negative LR
Hyperreflexia[57]	69%	88%	5.8	0.4

Adapted from McGee S, *Evidence Based Physical Diagnosis*, 2nd edn, St. Louis: Saunders, 2007.

Hyporeflexia and areflexia

DESCRIPTION

Stretch reflexes are decreased (i.e., hyporeflexia) or absent (i.e., areflexia) despite reinforcement manoeuvres (e.g. Jendrassik manoeuvre). Hyporeflexia is significant in the following clinical scenarios:[4]

1. hyporeflexia PLUS lower motor neuron signs (e.g. fasciculations, hypotonia, weakness)
2. asymmetric reflex amplitude.

The NINDS Muscle Stretch Reflex Scale describes a standardised method of grading reflexes (see Table 5.17).[48,120]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

UPPER MOTOR NEURON
→ Upper motor neuron
↓
→ Inhibitory interneuron

AFFERENT LIMB
⊗ Muscle spindle
↓
• Sensory afferent nerve
↓
• Nerve root
↓
• Dorsal horn grey matter
→ Inhibitory interneuron
↓

EFFERENT LIMB
• Anterior horn grey matter
↓
• Nerve root
⇒ Intervertebral foramen
⇒ Intervertebral disc
↓
• Peripheral nerve
⇒ Potential site of vulnerability
↓
× Muscle

CONDITION/S ASSOCIATED WITH

Common

- Normal variant
- Radiculopathy (e.g. spondylosis, osteoarthritis)
- Peripheral neuropathy

Less common

- Hyperacute spinal cord injury
- Guillain–Barré syndrome
- Poliomyelitis

MECHANISM/S

Hyporeflexia and areflexia are caused by:

1. peripheral neuropathy
2. radiculopathy
3. Guillain–Barré syndrome
4. disorders of the anterior horn cells
5. hyperacute upper motor neuron injury
6. normal variant.

Peripheral neuropathy

Compression mononeuropathy (e.g. carpal tunnel syndrome) results in a pattern of neurological deficits distal to the site of nerve injury. Common causes include carpal tunnel syndrome, common peroneal nerve palsy and radial nerve palsy (see Table 5.19). Length-dependent peripheral neuropathy is associated with the classic 'glove-and-stocking' distribution of sensory, motor and reflex findings. Sensory, motor and reflex abnormalities progressively increase as more proximal nerve fibres are affected. Common causes include diabetes mellitus, alcohol and drugs.

Radiculopathy

In disorders of the nerve root, hyporeflexia or areflexia often coexist with positive or negative sensory findings in a dermatomal distribution. Diminished reflexes are largely due to dysfunction of the afferent limb of the reflex arc.[121] In patients less than 45 years of age, the most common cause is intervertebral disc disease. In older patients the most common cause is spondylosis and osteophyte formation (see Table 5.20).[121]

Guillain–Barré syndrome

Acute inflammatory demyelinating polyradiculopathy (Guillain–Barré syndrome) causes areflexia in the distribution of the affected nerve roots. An ascending pattern of lower motor neuron findings is characteristic (e.g. hypotonia, weakness, areflexia).

Disorders of the anterior horn cells

Disorders of the anterior horn cells cause diminished reflexes due to dysfunction of the efferent limb of the reflex. Lower motor neuron findings are characteristic (e.g. wasting, fasciculations, hypotonia, weakness). Causes include motor neuron

TABLE 5.19 Reflex, motor and sensory findings in disorders of the peripheral nerves

Peripheral nerve	Reflex	Muscles/movement	Sensory	Causes of dysfunction
Axillary	None	Deltoid	Over deltoid	• Anterior shoulder dislocation • Fractured neck of humerus
Musculo-cutaneous	Biceps jerk	Biceps Brachialis	Lateral forearm	• Rare
Radial	Triceps jerk and supinator jerk	Triceps Wrist extensors Brachioradialis Supinator	Lateral dorsal forearm and back of thumb and index finger	• Crutch palsy • 'Saturday night palsy' • Fractured humerus • Entrapment in supinator muscle
Median	Finger jerk	Long finger flexors 1st, 2nd, 3rd digits Wrist flexors Pronator forearm Abductor pollicis brevis	Lateral palm, thumb and lateral 2 fingers, lateral half of 4th digit	• Carpal tunnel syndrome • Direct traumatic injury
Ulnar	None	Intrinsic hand muscles except abductor pollicis brevis, lateral 2 lumbicals, opponens policis, flexor policis brevis Flexor carpi ulnaris Long flexors 4th and 5th digits	Median palm, 5th digit, and medial half of 4th digit	• Trauma • Prolonged bed rest • Olecranon fracture • Ganglion of wrist joint
Obturator	Adductor reflex	Adductor	Medial surface thigh	• Pelvic neoplasm • Pregnancy
Femoral	Knee jerk	Knee extension	Antero-medial surface thigh and leg to medial malleolus	• Femoral hernia • Pregnancy • Pelvic hematoma • Psoas abscess
Sciatic, peroneal division	None	Ankle dorsiflexion and eversion	Anterior leg, dorsum ankle and foot	• Trauma at neck of fibula • Hip fracture or dislocation
Sciatic, tibial division	Ankle jerk	Plantarflexion and inversion	Posterior leg, sole and lateral border foot	• Rare

Adapted from Patten J, *Neurological Differential Diagnosis*, New York: Springer-Verlag, 1977; p 211.

TABLE 5.20 Reflex, motor and sensory findings in disorders of the cervical and lumbosacral nerve roots

Nerve root	Reflex	Muscles/movement	Sensory	Causes of dysfunction
C5	Biceps jerk	Deltoid Supraspinatus Infraspinatus Rhomboids	Lateral border upper arm	• Brachial neuritis • Cervical spondylosis • Upper brachial plexus avulsion
C6	Supinator jerk	Brachioradialis Brachialis	Lateral forearm including thumb	• Intervertebral disc lesion • Cervical spondylosis
C7	Triceps jerk	Latissimus dorsi Pectoralis major Triceps Wrist extensors Wrist flexors	Over triceps, mid-forearm and middle finger	• Intervertebral disc lesion • Cervical spondylosis
C8	Finger jerk	Finger flexors Finger extensors Flexor carpi ulnaris	Medial forearm and little finger	• Rare in disk lesions or spondylosis
T1	None	Intrinsic hand muscles	Axilla to olecranon	• Cervical rib • Thoracic outlet syndrome • Pancoast's tumour • Metastatic carcinoma
L2	None	Hip flexors	Across upper thigh	
L3	Adductor and knee jerk	Quadriceps and adductor	Across lower thigh	• Neurofibroma • Meningioma • Metastasis
L4	Knee jerk	Ankle inverters	Across to knee to medial malleolus	
L5	None	Ankle dorsiflexors	Leg to dorsum and sole of foot	• Disk prolapse • Metastases • Neurofibroma
S1	Ankle jerk	Ankle plantarflexor and everters	Behind lateral malleolus to lateral foot	• Disk prolapse • Metastases • Neurofibroma

Adapted from Patten J, *Neurological Differential Diagnosis*, New York: Springer-Verlag, 1977; p 211.

disease (e.g. amyotrophic lateral sclerosis), poliomyelitis and spinal muscular atrophy.

Hyperacute upper motor neuron injury

Acute spinal cord injury in the cervical and upper thoracic cord may result in areflexia, flaccid paralysis, complete sensory loss and sympathetic autonomic dysfunction below the level of the injury, resulting in a clinical syndrome known as spinal shock.[48] In the first 24 hours following spinal cord injury, spinal cord neurons are less excitable, likely due to decreased muscle spindle excitability and segmental input from afferent pathways caused by loss of tonic facilitation by gamma motor neurons.[48]

Normal variant

Diffusely decreased or absent reflexes, in isolation, do not necessarily represent neurological disease.[122,123] Decreased or absent reflexes are significant when accompanied by lower motor neuron signs (e.g. wasting, fasciculations, hypotonia,

weakness), in instances of asymmetrical reflexes or with other focal neurological signs.

SIGN VALUE

In several studies of patients without known pre-existing neurological disease, 6–50% of patients lack bilateral ankle jerk reflexes despite reinforcement maneouvres, and a small proportion of the population have generalised hyperreflexia.[4,122–126] The clinical utility of reflex examination findings in detecting cervical and lumbosacral radiculopathy is presented in Table 5.21.

TABLE 5.21 Clinical utility of reflex findings in cervical and lumbosacral nerve root dysfunction

Reflex examination	Sensitivity, %	Specificity, %	Positive LR	Negative LR
Decreased biceps or brachioradialis reflex, detecting C6 radiculopathy[127]	53	96	14.2	0.5
Decreased triceps reflex, detecting C7 radiculopathy[127,128]	15–65	81–93	3.0	NS
Asymmetric quadriceps reflex, detecting L3 or L4 radiculopathy[129–131]	30–57	93–96	8.7	0.6
Asymmetric ankle jerk reflex, detecting S1 radiculopathy[36,129–132]	45–91	53–94	2.9	0.4

Adapted from McGee S, *Evidence Based Physical Diagnosis*, 2nd edn, St. Louis: Saunders, 2007.

Hypotonia

DESCRIPTION

Hypotonia is decreased resistance to passive movement due to decreased resting muscle tone. The limb may feel 'floppy', the outstretched arm when tapped may demonstrate wider than normal excursions, and the knee jerk may be abnormally pendular (i.e., swings more).[4,18]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

LOWER MOTOR NEURON

- Anterior horn grey matter, spinal cord
- ↓
- Nerve root
- ⇒ Intervertebral disc
- ⇒ Intervertebral foramen
- ↓
- Nerve plexus (e.g. brachial plexus)
- ↓
- Peripheral nerve
- ⇒ Potential sites of nerve entrapment (e.g. carpal tunnel)

CEREBELLUM

- Vermis and flocculonodular lobe
- → Anterior corticospinal tract
- → Reticulospinal tract
- → Vestibulospinal tract
- → Tectospinal tract
- Paravermal (intermediate) hemisphere
- → Lateral corticospinal tract
- → Rubrospinal tract
- Lateral hemisphere
- → Lateral corticospinal tract

CONDITION/S ASSOCIATED WITH

Common

- Radiculopathy
- Peripheral neuropathy
- Cerebellar infarction
- Cerebellar haemorrhage
- Hyperacute spinal cord injury

Less common

- Guillain–Barré syndrome
- Spinal muscular atrophy
- Poliomyelitis
- Botulism

MECHANISM/S

Hypotonia is caused by:

1. lower motor neuron disorders
2. cerebellar disorders
3. hyperacute upper motor neuron disorders
4. toxic and infectious disorders (e.g. botulism).

Lower motor neuron disorders

Muscle denervation results in decreased resting muscle tone and flaccid paresis. Lower motor neurons are the final common pathway in skeletal muscle innervation.[57] Causes include radiculopathy, peripheral neuropathy and Guillain–Barré syndrome. Associated features of lower motor neuron disease include wasting, fasciculations, weakness and hyporeflexia or areflexia.

Cerebellar disorders

The mechanism of hypotonia in cerebellar lesions is not known. Hypotonia in cerebellar disease may result from a relative paucity of neural input to the descending motor tracts (e.g. anterior corticospinal tract, reticulospinal tract, vestibulospinal tract, tectospinal tracts). Associated features of cerebellar disease include dysdiadochokinesis, intention tremor, dysmetria, nystagmus and dysarthria.

Hyperacute upper motor neuron disorders

Acute stroke and/or spinal cord injury may result in hypotonia and flaccid paresis immediately following injury. Spasticity and spastic paresis develop days to weeks later.[55] Acute spinal cord injury in the cervical and upper thoracic cord may cause hypotonia, areflexia, flaccid paralysis, complete sensory loss and autonomic dysfunction below the level of the injury, resulting in a clinical syndrome known as spinal shock.[48] The exact mechanism of spinal shock is unknown. In the first 24 hours following spinal cord injury, spinal cord neurons are less excitable, likely due to decreased muscle spindle excitability and segmental input from afferent pathways caused by loss of tonic facilitation by gamma motor neurons.[48]

Toxic and infectious disorders

Botulism is caused by the bacterium *Clostridium botulinum*, which produces a toxin that blocks the release of acetylcholine at the motor terminal.[133]

SIGN VALUE

Hypotonia is most commonly a lower motor neuron sign. In a group of 444 patients with unilateral cerebellar lesions, hypotonia was present in 76% of patients.[4,29,30]

Less commonly, it may be a sign of cerebellar dysfunction or hyperacute upper motor neuron dysfunction.

Intention tremor

DESCRIPTION

Intention tremor is a slow (2- to 4-Hz) tremor during voluntary movement that develops as the limb approaches the target.[41,68] Tests to assess target seeking, such as the finger-to-nose test and heel-to-shin test, are performed to detect intention tremor.[68]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

CEREBELLUM

- Vermis and flocculonodular lobe
  - → Anterior corticospinal tract
  - → Reticulospinal tract
  - → Vestibulospinal tract
  - → Tectospinal tract
- Paravermal (intermediate) hemisphere
  - → Lateral corticospinal tract
  - → Rubrospinal tract
- Lateral hemisphere
  - → Lateral corticospinal tract

CONDITION/S ASSOCIATED WITH

Common

- Cerebellar infarction
- Cerebellar haemorrhage
- Alcohol misuse
- Drugs (e.g. benzodiazepines, lithium, phenytoin)
- Multiple sclerosis

Less common

- Hereditary cerebellar degeneration (e.g. Freidreich's ataxia)
- Mass lesion (e.g. tumour, abscess, AVM)
- HSV cerebellitis
- Paraneoplastic cerebellar degeneration

MECHANISM/S

Intention tremor is an ipsilateral hemispheric cerebellar sign. Lesions of the intermediate and lateral cerebellar hemispheres may cause slow, uncoordinated and clumsy movements of the ipsilateral distal extremity that are aggravated during attempted target localisation tasks (see Table 5.22).[4] The

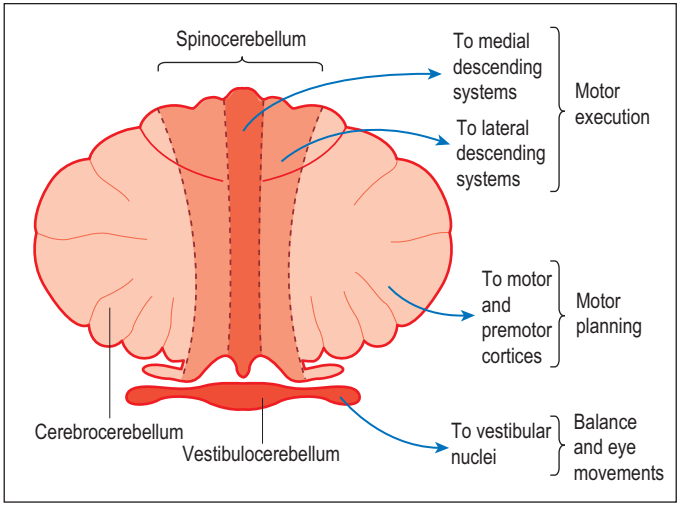


Figure 5.55 Functional anatomy of the cerebellum

Reproduced, with permission, from Barrett KE, Barman SM, Boitano S et al. *Ganong's Review of Medical Physiology*, 23rd edn. Available: http://accessmedicine.com [9 Dec 2010].

TABLE 5.22 Functional anatomy of the cerebellum and associated motor pathways

Cerebellar anatomy	Function	Associated motor pathways
Intermediate hemisphere	• Distal limb coordination	• Lateral corticospinal tracts • Rubrospinal tracts
Lateral hemisphere	• Motor planning, distal extremities	• Lateral corticospinal tracts

Adapted from Blumenfeld H, *Neuroanatomy Through Clinical Cases*, Sunderland: Sinauer, 2002.

oscillations result from uncoordinated contractions predominantly of the proximal limb musculature perpendicular to the axis of motion.[68] Delays in motor initiation and movement termination, and abnormalities of movement force and acceleration, contribute to intention tremor.[67]

SIGN VALUE

Intention tremor is an ipsilateral hemispheric cerebellar sign. In two studies of patients with unilateral cerebellar lesions, intention tremor was present in 29%.[4,29,30]

Internuclear ophthalmoplegia (INO)

DESCRIPTION

Internuclear ophthalmoplegia (INO) is characterised by impaired adduction of the eye on the abnormal side and horizontal jerk nystagmus in the opposite eye on lateral gaze away from the side of the lesion. The remainder of the extraocular movements, including convergence, are normal.[4,134]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

- Abducens nuclei, pons
- ↓
- ∅ Medial longitudinal fasciculus (MLF)
- ↓
- Oculomotor nuclei, midbrain

CONDITION/S ASSOCIATED WITH[134–138]

- Multiple sclerosis
- Dorsal pontine infarction

MECHANISM – INTERNUCLEAR OPHTHALMOPLEGIA (INO)

INO is caused by a lesion in the medial longitudinal fasciculus (MLF). The MLF connects the abducens nerve (CNVI) nuclei to the oculomotor nerve (CNIII) nuclei and facilitates conjugate eye movements during lateral gaze by coordinating adduction with abduction.[134] INO should be differentiated from peripheral causes of isolated medial rectus paresis (this is called pseudo-internuclear ophthalmoplegia) including partial oculomotor nerve palsy, myasthenia gravis, Miller Fisher's syndrome and disorders of the medial rectus muscle.[134]

SIGN VALUE

In a study of patients with bilateral INO, multiple sclerosis was present in 97% of patients. The most common cause of unilateral INO was vertebrobasilar territory ischaemia.[139]

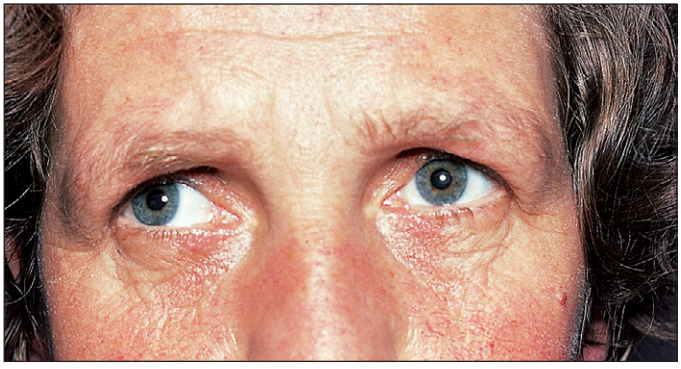


Figure 5.56 Right lateral gaze with evidence of left adduction paresis in a patient with internuclear ophthalmoplegia

Reproduced, with permission, from Miley JT, Rodriguez GJ, Hernandez EM et al, Neurology 2008; 70(1): e3–e4, Fig 1.

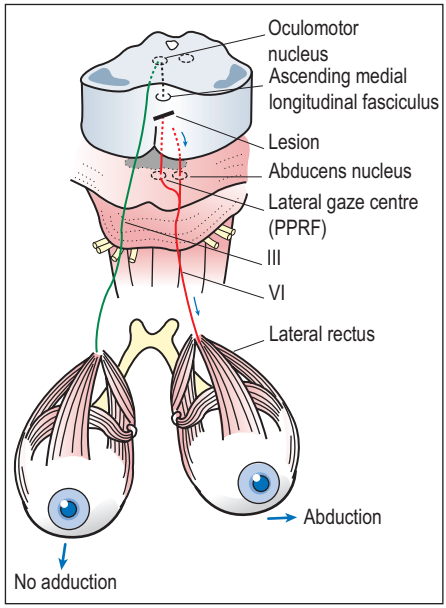


Figure 5.57 Schematic representation of the abducens nuclei, medial longitudinal fasciculus (MLF) and oculomotor nuclei pathways involved in internuclear ophthalmoplegia

PPRF = paramedian pontine reticular formation.

Based on Medscape, Overview of vertebrobasilar stroke. Available: http://emedicine.medscape.com/article/323409-media [5 Apr 2011].

Jaw jerk reflex

DESCRIPTION

Percussion of the chin causes contraction of the masseter muscles due to activation of a monosynaptic stretch reflex.[6,57] The jaw jerk reflex may be present in a proportion of normal individuals without neurological disease.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[6]

AFFERENT LIMB

⊗ Muscle spindle

↓

• Mandibular branch trigeminal nerve (CNV V3)

⇒ Foramen ovale

↓

• Trigeminal (Gasserian) ganglion

⇒ Meckel's cave, petrous bone

↓

• Mesencephalic trigeminal nucleus

↓

EFFERENT LIMB

• Motor trigeminal nucleus, pons

↓

• Trigeminal (Gasserian) ganglion

⇒ Meckel's cave, petrous bone

⇒ Foramen ovale

↓

• Mandibular branch trigeminal nerve (CNV V3)

↓

× Masseter muscle

CONDITION/S ASSOCIATED WITH[6,57,107,140]

Common

- Normal variant
- Diffuse white matter disease (e.g. lacunar infarction)
- Vascular dementia

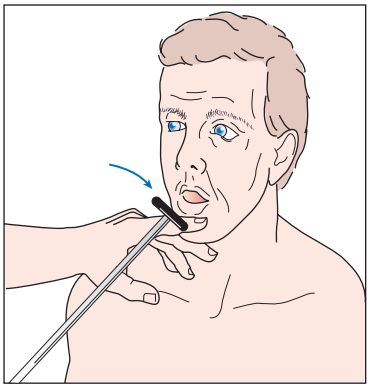


Figure 5.58 Jaw jerk reflex

Reproduced, with permission, from Walker HK, Hall WD, Hurst JW, *Clinical Methods: The History, Physical, and Laboratory Examinations*, 3rd edn, Boston: Butterworths, 1990: Fig 50.2.

Less common

- Motor neuron disease (e.g. amyotrophic lateral sclerosis)
- Bilateral cerebral infarction
- Multiple sclerosis
- Progressive multifocal leucoencephalopathy
- Central pontine myelinolysis

MECHANISM/S

A brisk jaw jerk reflex is a sign of bilateral upper motor neuron disease. Loss of supranuclear innervation of the motor trigeminal nucleus causes hyperexcitability of alpha motor neurons innervating the masseter muscles (i.e., hyperreflexia, see 'Hyperreflexia' in this chapter).[107]

SIGN VALUE

A brisk jaw jerk reflex is a sign of bilateral upper motor neuron disease above the pons.

Light–near dissociation

DESCRIPTION

Light–near dissociation is characterised by:[9]

1. normal accommodation response (pupils constrict to near stimuli)
2. sluggish or absent pupillary light response.

Light–near dissociation is said to be present if the near pupillary response (tested in moderate light) exceeds the best pupillary response with a bright light source.[9] Light–near dissociation is associated with Argyll Robertson pupils (see 'Argyll Robertson pupils' in this chapter).

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[9]

Accommodation and pupillary light pathways

AFFERENT STRUCTURES

- Retinal neuroepithelium
- ↓
- Optic nerve (CNII)
- ↓
- Pretectal nucleus midbrain
- ↓
- ↔ Bilateral innervation of Edinger–Westphal nuclei
- ↓

EFFERENT STRUCTURES

- Visual cortex (accommodation only)
- ↓
- Accommodation area, visual cortex (accommodation only)
- ↓
- Pretectal nuclei, midbrain
- ⇒ Pineal gland
- ↓
- Edinger–Westphal nuclei, midbrain
- ↓
- Oculomotor nerve (CNIII)
- ↓
- Ciliary ganglion
- ↓
- Short ciliary nerves
- ↓
- × Pupillary constrictor muscles
- × Ciliary muscle
- × Medial rectus muscles

CONDITION/S ASSOCIATED WITH[4,9]

Common

- Dorsal midbrain lesion
- Argyll Robertson pupils

Less common

- Pinealoma
- Hydrocephalus
- Multiple sclerosis
- Neurosarcoidosis
- Adie's tonic pupil

MECHANISM/S

Causes of light–near dissociation include:

1. dorsal midbrain lesion
2. Adie's tonic pupil
3. Argyll Robertson pupils.

Dorsal midbrain lesion

Loss of pretectal light input to oculomotor nuclei, due to a lesion in the tectum of the midbrain, results in impaired pupillary response with preservation of the accommodation pathways. Dorsal midbrain syndrome (Parinaud's syndrome) is a clinical syndrome associated with a lesion of the posterior commissure and interstitial nucleus characterised by:[7,13,141]

1. vertical gaze palsy
2. normal to large pupils with light–near dissociation
3. convergence–retraction nystagmus
4. eyelid retraction.

Adie's tonic pupil

The four characteristics of Adie's tonic pupil are:[4,14–16]

1. unilateral mydriasis
2. decreased or absent pupillary light reaction
3. delayed near–light reaction in pupillary constriction and accommodation
4. pupillary constrictor sensitivity to pilocarpine.

Adie's tonic pupil is caused by injury to the ciliary ganglion and/or postganglionic fibres and results in abnormal regrowth of the short ciliary nerves.[4] Normally, the ciliary ganglion sends 30 times more nerve fibres to the ciliary muscle than to the pupillary constrictor muscle.[14–16] Aberrant regrowth of the ciliary nerves (a random process) favours reinnervation of the pupillary sphincter rather than the ciliary muscle, with the 30:1 ratio reversed, resulting in the abnormal pupil properties seen in this sign.[4] Causes of Adie's tonic

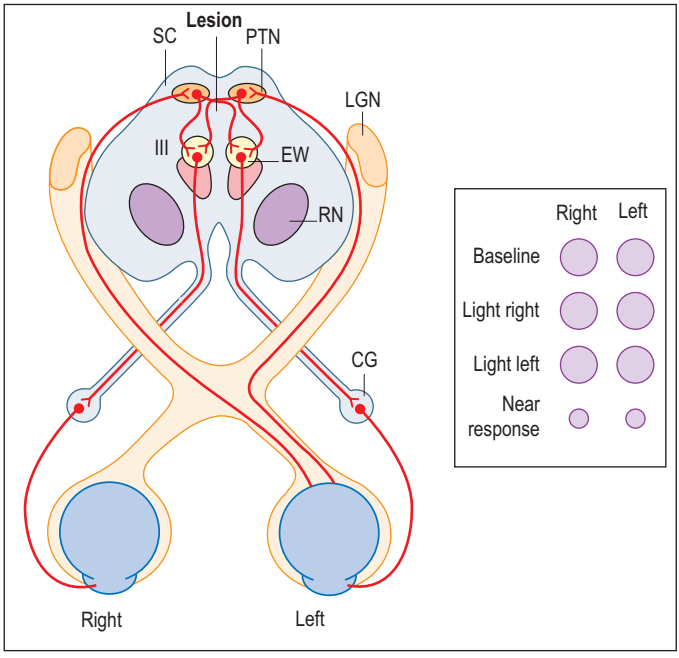


Figure 5.59 Pupillary response associated with light–near dissociation due to lesion in the pretectum

CG = ciliary ganglion; EW = Edinger–Westphal nucleus; LGN = lateral geniculate nucleus; PTN = pretectal nucleus; RN = red nucleus; SC = superior colliculus.

Reproduced, with permission, from Goldman L, Ausiello D, *Cecil Medicine*, 23rd edn, Philadelphia: Saunders, 2007: Fig 450-2.

pupil include orbital trauma, orbital tumours and varicella zoster infection in the ophthalmic division of the trigeminal nerve.[4]

Argyll Robertson pupils

See 'Argyll Robertson pupils' in this chapter.

SIGN VALUE

Light–near dissociation is associated with a dorsal midbrain lesion. It is classically associated with tertiary syphilis in Argyll Robertson pupils.

Myotonia – percussion, grip

DESCRIPTION

Percussion myotonia is a sustained muscle contraction following percussion of a muscle.[4] Grip myotonia is a sustained muscle contraction following forceful contraction of the hand muscles.[4]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[142–144]

× Muscle ion channels

CONDITION/S ASSOCIATED WITH

Common

- Myotonic dystrophy

Less common

- Myotonia congenita
- Paramyotonia congenita

MECHANISM/S

Myotonia results from electrical instability of the sarcolemma membrane causing prolonged depolarisation of the muscle fibres. Causes include:

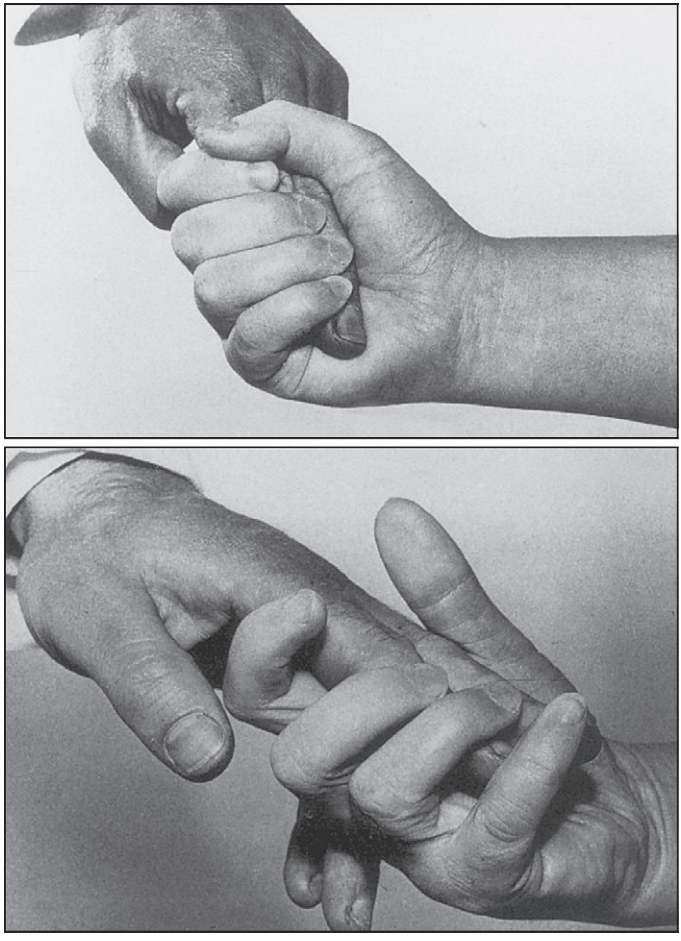


Figure 5.60 Grip myotonia

Reproduced, with permission, from Libby P, Bonow RO, Mann DL, Zipes DP, *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 8th edn, Philadelphia: Saunders, 2007: Fig 87-7.

1 myotonia congenita
2 myotonic dystrophy
3 paramyotonia congenita.

Myotonia congenita

In myotonia congenita, abnormal sarcolemmal chloride channels cause prolonged depolarisation of the sarcolemmal membrane and muscle hyperexcitability.[142]

Myotonic dystrophy

Myotonic dystrophy is a trinucleotide repeat disorder, which is likely caused by abnormal gene transcription of the genes adjacent to the myotonic dystrophy protein kinase (MDPK) gene on chromosome 19q13.3.[143] Studies have shown that abnormally transcribed mRNA is directly toxic and causes abnormal splicing variants in various mRNA transcripts, including a muscle chloride ion channel.[144] Disease progression causes worsening muscle weakness, and the myotonia may eventually disappear in severely affected muscle groups.[143]

Paramyotonia congenita

Paramyotonia congenita is a form of potassium-sensitive myotonia. It is caused by a mutation in a gene encoding a sodium channel on chromosome 17q.[142] The myotonia typically affects the muscles of the face and hands and is exacerbated by repetitive exercise and cold temperatures.[143]

SIGN VALUE

Myotonia is associated with ion channel disorders (i.e., 'channelopathies').

Oculomotor nerve (CNIII) palsy

DESCRIPTION

Oculomotor nerve (CNIII) palsy is characterised by the following findings in the primary gaze position:[4]

1. hypotropia (eye deviated down)
2. exotropia (eye deviated out)
3. ptosis
4. mydriasis.

There is impaired elevation, depression, adduction and extorsion of the affected eye.

Oculomotor nerve palsy can be complete (i.e., gaze paresis, ptosis, mydriasis), pupil sparing (i.e., gaze paresis, ptosis) or with isolated pupil involvement (i.e., mydriasis only).

CONDITION/S ASSOCIATED WITH[1,145–150]

Common

- Posterior communicating (PComm) artery aneurysm
- Diabetic mononeuropathy/ microvascular infarction
- Uncal herniation

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

- Edinger–Westphal nuclei, midbrain
  ↓
- Oculomotor nuclei, midbrain
  ↓
- Oculomotor nerve

⇒ Posterior communicating (PComm) artery, circle of Willis

⇒ Uncus, medial temporal lobe

⇒ Subarachnoid space

⇒ Superior orbital fissure

⇒ Cavernous sinus

⇒ Orbital apex

↓

× EOMs: medial rectus, superior rectus, inferior rectus, inferior oblique muscles

× Pupillary constrictor muscle

× Levator palpebrae muscle

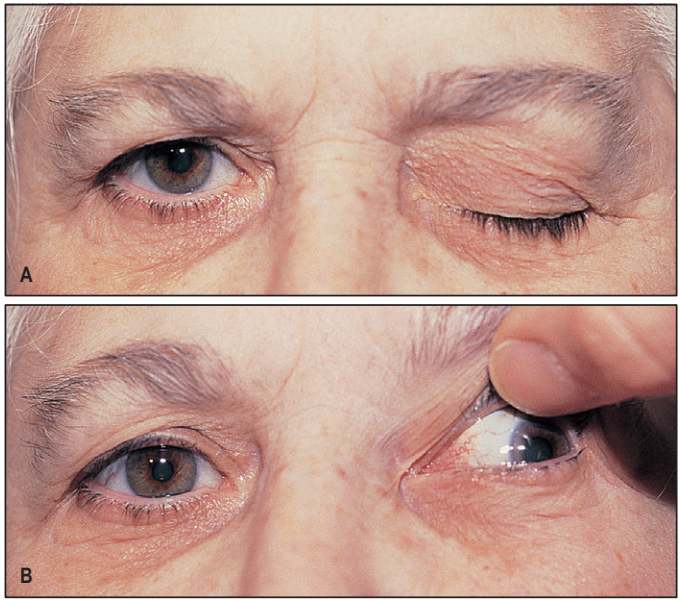


Figure 5.61 Complete oculomotor nerve (CNIII) palsy

A, Complete left ptosis; **B**, left exotropia and hypotropia.

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 11-10-2.

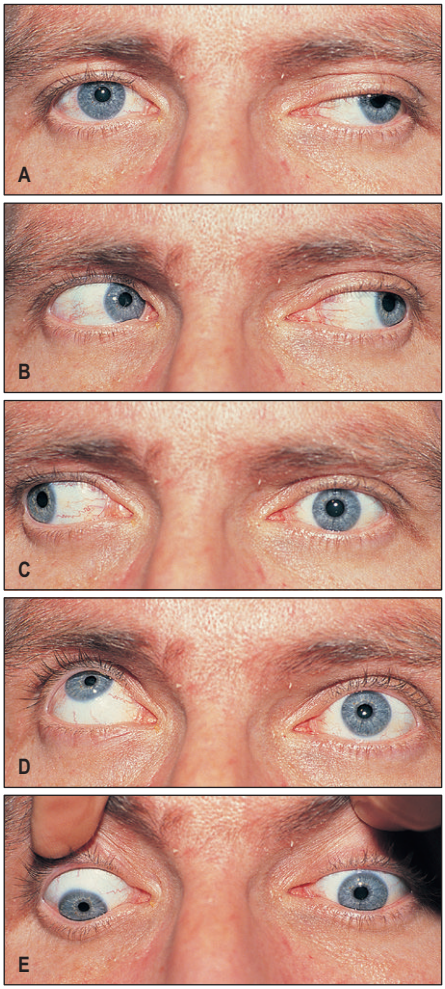


Figure 5.62 Partial left oculomotor nerve (CNIII) palsy

A, Primary gaze position, with mild ptosis, exotropia, hypotropia, mild mydriasis of left eye; **B**, normal left gaze; **C**, right gaze with impaired adduction left eye; **D**, upward gaze with poor elevation left eye; **E**, downward gaze with impaired depression left eye.

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 11-10-1.

Less common

- Ophthalmoplegic migraine (transient)
- Cavernous sinus syndrome
- Orbital apex syndrome

MECHANISM/S

Complete oculomotor nerve palsy

The oculomotor nerve innervates all of the extraocular muscles except the superior oblique and lateral rectus muscles. Weakness of the pupillary constrictor muscles and levator palpebrae muscle causes mydriasis and ptosis, respectively. Mechanisms of clinical findings in oculomotor nerve palsy are listed in Table 5.23.

Oculomotor nerve palsy with pupil sparing

The central fibres of the oculomotor nerve are more vulnerable to microvascular infarction. A lesion limited to the central fibres of the oculomotor nerve may result in oculomotor nerve palsy with pupillary sparing.

Oculomotor nerve palsy with isolated pupil involvement

The fibres of the oculomotor nerve innervating the pupillary constrictor muscle are located superomedially near the nerve surface and are particularly prone to compressive lesions.[1,149] Compressive peripheral lesions of the oculomotor nerve may initially manifest with isolated pupil involvement.

In general, causes of oculomotor nerve (CNIII) palsy include:

1. disorders of the nerve segment in the subarachnoid space
2. diabetic mononeuropathy and microvascular infarction
3. cavernous sinus syndrome
4. orbital apex syndrome
5. brainstem lesion (rare).

Disorders of the nerve segment in the subarachnoid space

Compression of the oculomotor nerve spanning the subarachnoid space is caused by mass lesions (e.g. tumour, abscess),

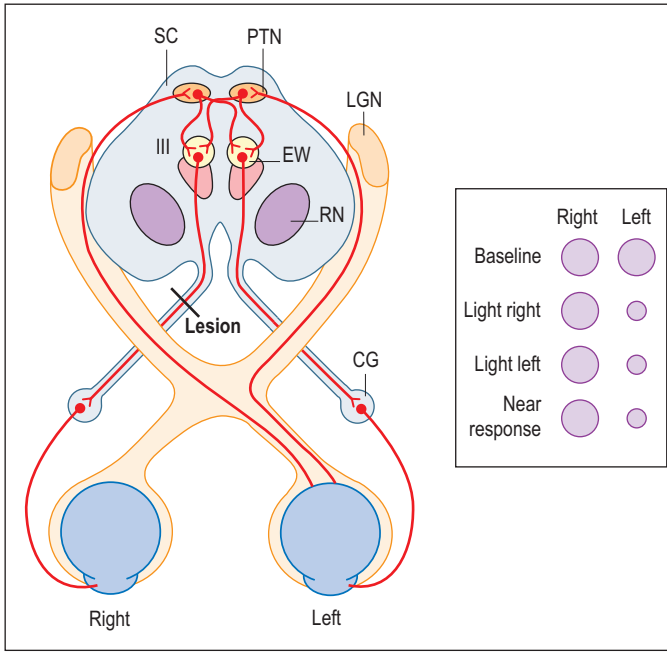


Figure 5.63 Pupillary response associated with oculomotor nerve palsy

CG = ciliary ganglion; EW = Edinger–Westphal nucleus; LGN = lateral geniculate nucleus; PTN = pretectal nucleus; RN = red nucleus; SC = superior colliculus.

Reproduced, with permission, from Goldman L, Ausiello D, *Cecil Medicine*, 23rd edn, Philadelphia: Saunders, 2007: Fig 450-2.

posterior communicating (PComm) artery aneurysm and uncal herniation.

POSTERIOR COMMUNICATING (PCOMM) ARTERY ANEURYSM

The oculomotor nerve exits the midbrain adjacent to the posterior communicating artery (PComm), posterior cerebral artery (PCA) and superior cerebellar arteries (SCAs). Aneurysms of any of these arteries can cause oculomotor nerve palsy. Aneurysms of the PComm artery are the most common.[147] Early diagnosis is potentially life-saving, as there is a significant risk of subarachnoid haemorrhage.

UNCAL HERNIATION (HUTCHINSON'S PUPIL)

See 'Hutchinson's pupil' in this chapter.

Diabetic mononeuropathy and microvascular infarction

Diabetes mellitus causes various cranial mononeuropathies due to diabetic vasculopathy of the vasa nervorum (i.e., disease of the blood supply of the peripheral nerve), resulting in microvascular infarction of the nerve.[3]

Cavernous sinus syndrome

See 'Cavernous sinus syndrome' in this chapter.

Orbital apex syndrome

See 'Orbital apex syndrome' in this chapter.

Brainstem lesion

Brainstem lesions affecting the oculomotor nuclei and Edinger–Westphal nuclei may result in complete oculomotor nerve palsy. Causes include midbrain vascular syndromes, multiple sclerosis and tumours.

SIGN VALUE

In a group of a patients with oculomotor nerve palsy, 95% with aneurysmal causes had abnormal pupil findings (e.g. mydriasis, abnormal light reflex). 73% of patients with microvascular infarction of the oculomotor nerve demonstated a pupil-sparing oculomotor nerve (CNIII) palsy.[149–156] Refer to Table 5.24 for causes by age group.

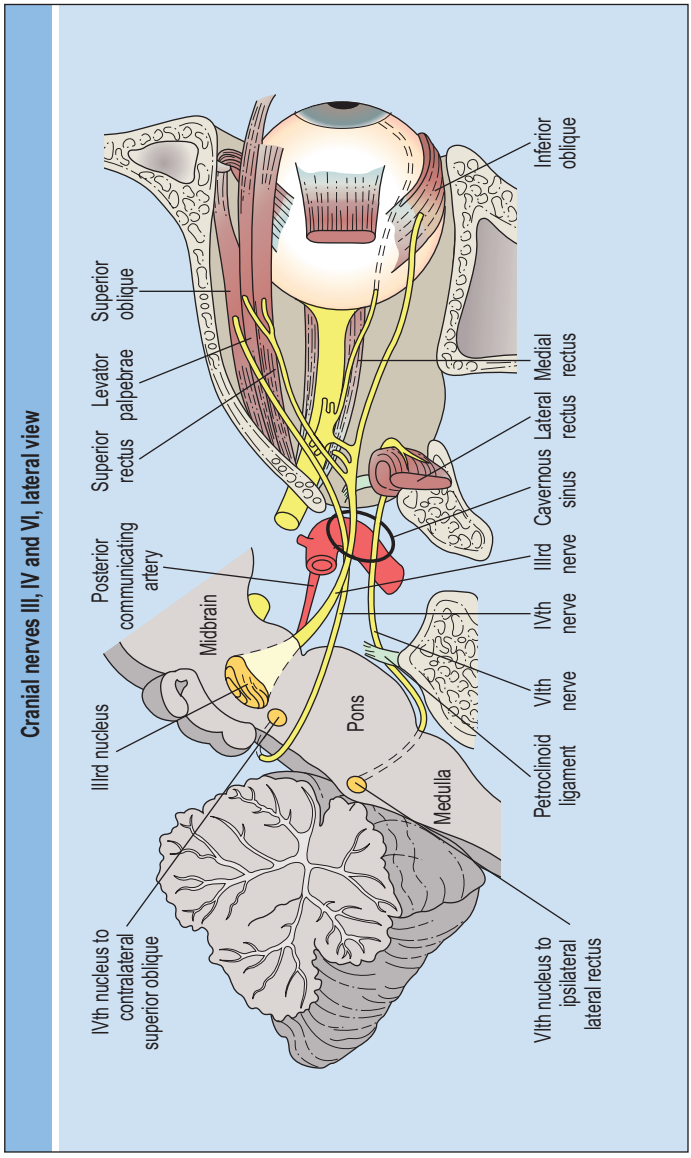


Figure 5.64 Anatomy of the oculomotor nerve (CNIII), lateral view

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 9-15-1.

TABLE 5.23 Mechanism of the clinical features of oculomotor nerve (CNIII) palsy

Feature of oculomotor nerve palsy	Mechanism
• Hypotropia	→ Unopposed superior oblique muscle
• Exotropia	→ Unopposed lateral rectus muscle
• Ptosis	→ Levator palpebrae weakness
• Mydriasis	→ Pupillary constrictor muscle weakness
• Impaired elevation	→ Superior rectus muscle weakness
• Impaired depression	→ Inferior rectus muscle weakness
• Impaired adduction	→ Medial rectus muscle weakness
• Impaired extorsion	→ Inferior oblique muscle weakness

TABLE 5.24 Causes of acquired third nerve palsy

Cause(s)	Adults (%)
Trauma	14
Neoplasm	11
Aneurysm	12
Vascular/diabetic	23
Other	16
Idiopathic	24

Adapted from Kodsi SR, Younge BR, Acquired oculomotor, trochlear, and abducent cranial nerve palsies in pediatric patients, Am J Ophthalmol 1992; 114: 568–574.

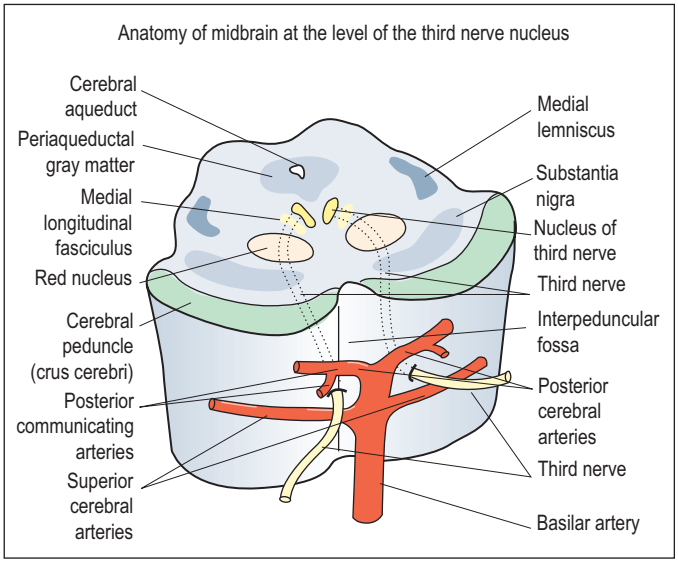


Figure 5.65 Neuroanatomy of the oculomotor nerve brainstem exit points, including the posterior cerebral arteries, posterior communicating arteries and superior cerebellar arteries

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 9-14-2.

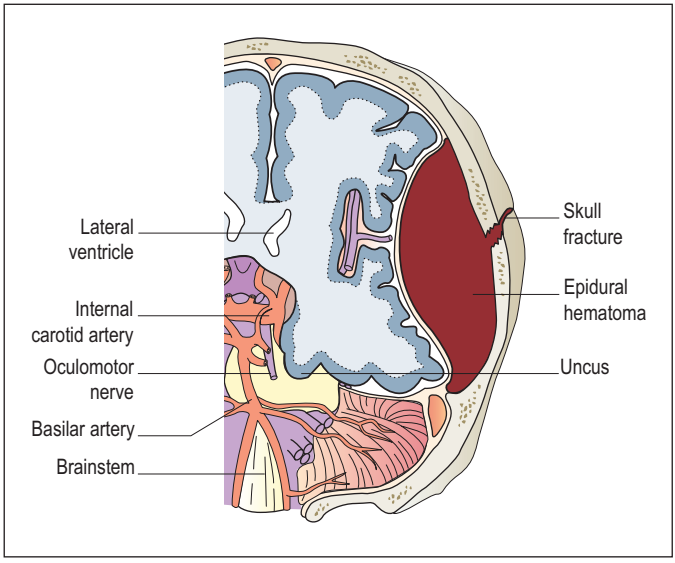


Figure 5.66 Schematic representation of uncal herniation resulting in oculomotor nerve compression

Reproduced, with permission, from Marx JA, Hockberger RS, Walls RM et al. *Rosen's Emergency Medicine*, 7th edn, Philadelphia: Mosby, 2010: Fig 38-5.

Optic atrophy

DESCRIPTION

The optic disc appears asymmetrical, smaller in size, and is a pale white color.[18]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

- Optic nerve
- ⇒ Orbital apex
- ⇒ Optic canal
- ⇒ Subarachnoid space

CONDITION/S ASSOCIATED WITH[157,158]

Common

- Anterior ischaemic optic neuropathy (AION)
- Multiple sclerosis

Less common

- Chronic optic neuritis
- Glaucoma
- Tumour
- Thyroid eye disease
- Leber's hereditary optic neuropathy

MECHANISM/S

Optic atrophy is caused by a long-standing lesion of the optic nerve or by increased intracranial pressure. The patient may have associated bedside clinical evidence of optic nerve dysfunction (e.g. decreased visual acuity, central scotoma).[158]

SIGN VALUE

Optic atrophy is caused by degeneration of the fibres of the optic nerve due to a lesion of the optic nerve of at least 4–6 weeks duration.[158,159]

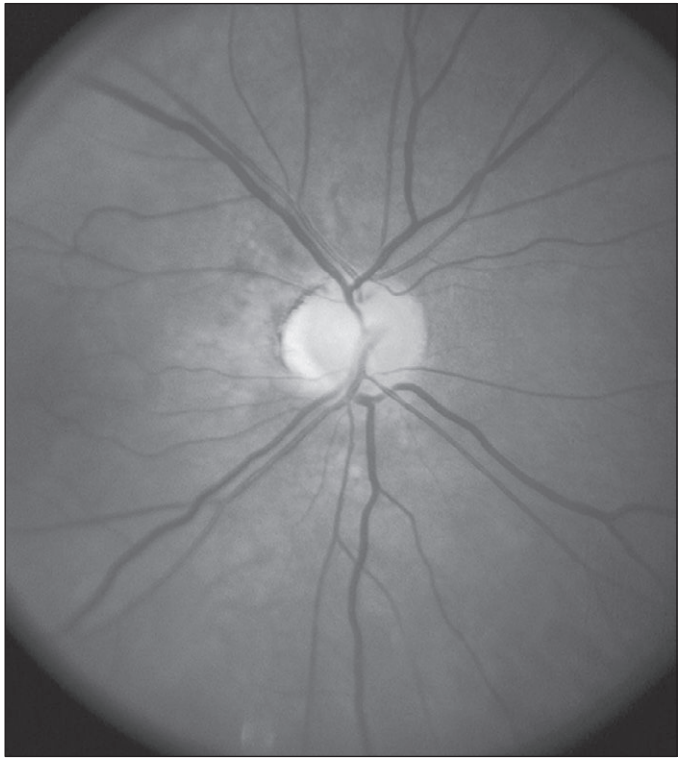


Figure 5.67 Optic atrophy

Reproduced, with permission, from Isaacson RS, Optic atrophy. In: Ferri FF, *Clinical Advisor 2011*. Philadelphia: Mosby, 2011: Fig 1-220.

Orbital apex syndrome

DESCRIPTION

Orbital apex syndrome is a cranial nerve syndrome associated with proptosis, involving the contents of the orbital apex:[6,49]

1. optic nerve (CNII)
2. oculomotor nerve (CNIII)
3. trochlear nerve (CNIV)
4. ophthalmic division of the trigeminal nerve (CNV V1)
5. abducens nerve (CNVI)
6. sympathetic fibres.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

ORBITAL APEX CONTENTS

- Optic nerve (CNII)
- Oculomotor nerve (CNIII)
- Trochlear nerve (CNIV)
- Ophthalmic division (V1) trigeminal nerve (CNV)
- Abducens nerve (CNVI)
- Sympathetic plexus

⇒ Venous plexus

⇒ Periorbital soft tissue

CONDITION/S ASSOCIATED WITH[6,49]

Common

- Tolosa–Hunt syndrome
- Orbital granuloma

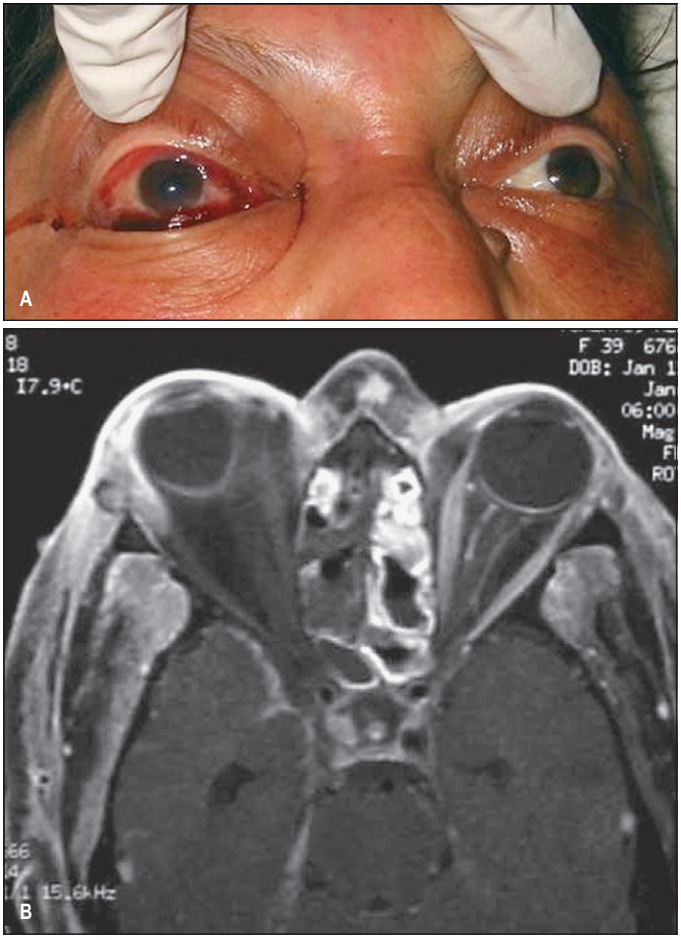


Figure 5.68 Patient with rhinocerebral mucormycosis resulting in orbital apex syndrome

A, Patient with prominent right proptosis and ophthalmoplegia; **B**, MRI of right retro-orbital infectious mass.

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 9-23-1.

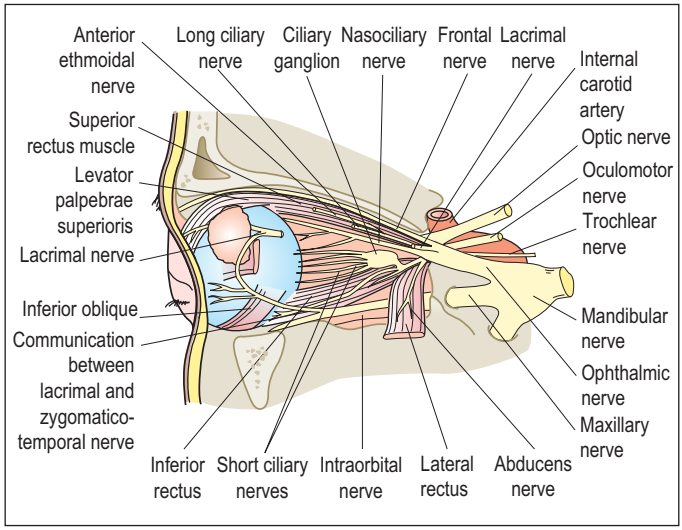


Figure 5.69 Anatomy of the contents of the orbital apex

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 74-1.

TABLE 5.25 Mechanisms of clinical signs in orbital apex syndrome

Clinical signs and sequelae	Cranial nerve dysfunction
• Decreased visual acuity, afferent pupillary defect, decreased colour vision, decreased brightness sense	→ Optic nerve (CNII)
• Extraocular muscle paresis • Mydriasis and poorly reactive pupil • Ptosis	→ Oculomotor nerve (CNIII)
• Superior oblique muscle paresis	→ Trochlear nerve (CNIV)
• Hypoaesthesia or anaesthesia distribution ophthalmic nerve • Decreased corneal sensation	→ Ophthalmic branch, trigeminal nerve (CNV V1)
• Abducens muscle paresis	→ Abducens nerve (CNVI)

Less common

- Rhinocerebral mucormycosis
- Retrobulbar haemorrhage
- Graves' ophthalmopathy

MECHANISM/S

Typically, an enlarging infectious or inflammatory mass at the orbital apex leads to proptosis and pain. Proptosis is related to mass effect on the orbital contents.[49] Unlike in cavernous sinus syndrome, patients typically have early involvement of the optic nerve (CNII) with evidence of visual loss or an afferent pupillary defect.[6,49] The mechanisms of clinical features in orbital apex syndrome are listed in Table 5.25.

SIGN VALUE

Orbital apex syndrome is an emergency and has a high rate of morbidity and mortality.

Palmomental reflex

DESCRIPTION

The palmomental reflex is characterised by ipsilateral contraction of the mentalis muscle resulting in ipsilateral lower lip protrusion or wrinkling, when the examiner strokes the patient's thenar eminence.[4] The palmomental reflex is a primitive reflex that is normally present in infancy.[4] The reflex may reappear later in life due to frontal lobe disease or normal ageing.[97]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

- Frontal lobes

CONDITION/S ASSOCIATED WITH

Common

- Normal variant
- Alzheimer's dementia
- Frontotemporal dementia
- Vascular dementia

Less common

- Parkinson's disease
- Advanced HIV/AIDS

MECHANISM/S

The mechanism of re-emergence of the palmomental reflex is unknown. The reflex is likely controlled by nonprimary motor cortical areas, which exert an inhibitory control of the spinal reflex.[160] Damage to these areas may result in disinhibition and thus 'release' the reflex.[90,160]

SIGN VALUE

In a study of 39 patients with a unilateral palmomental reflex, an ipsilateral cerebral hemisphere lesion was found in 44%, a contralateral lesion in 36%, bilateral lesions in 10% and no lesions were found in 10%.[161] The side of the reflex does not correlate with the side of the lesion.[161] The palmomental sign may be present in approximately 3–70% of normal subjects.[4,92–94,162–165]

Papilloedema

DESCRIPTION

Papilloedema is swelling and blurring of the optic disc margins.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

- Optic disc
  ↓
- Optic nerve
- ⇒ Optic canal
- ⇒ Orbital apex
- ⇒ Cavernous sinus
- ⇒ Subarachnoid space
- ⇒ Midbrain

CONDITION/S ASSOCIATED WITH

Common

- Optic neuritis
- Elevated intracranial pressure (e.g. idiopathic intracranial hypertension)
- Drugs (e.g. ethambutol, chloramphenicol)

Less common

- Mass lesion (e.g. tumour, abscess, AVM)
- Hydrocephalus

MECHANISM/S

Papilloedema is caused by increased intracranial pressure or a compression lesion of the optic nerve. Disc swelling papilloedema results from blockage of axoplasmic flow in neurons of the optic nerve, resulting in swelling of the axoplasm of the optic disc.[159] Papilloedema is associated with other signs of optic nerve dysfunction (e.g. decreased visual acuity, relative afferent pupillary defect [RAPD], visual field defects). The most common visual field defects in acute papilloedema are enlargement of the physiological blindspot, concentric constriction and inferior nasal field loss.[159]

SIGN VALUE

Papilloedema is a sign of optic nerve (CNII) swelling due to a compressive optic nerve lesion or increased intracranial pressure.

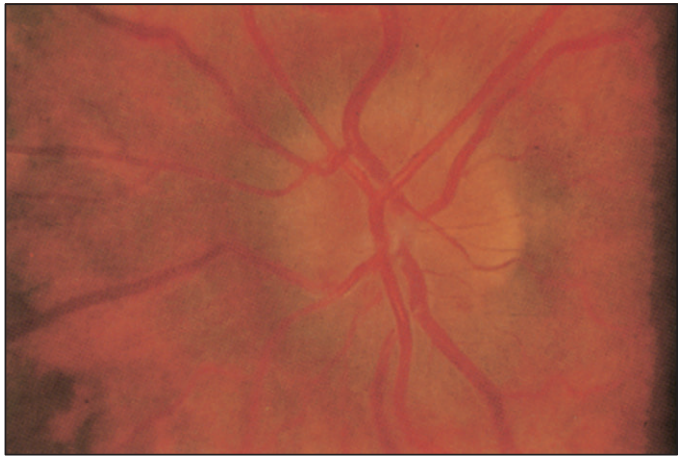


Figure 5.70 Swollen optic disc in early papilloedema

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 15-9.

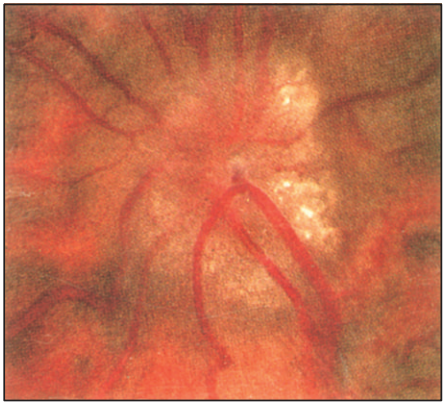


Figure 5.71 Chronic papilloedema with marked disc elevation and gliosis

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 15-11.

Parkinsonian gait

DESCRIPTION

The parkinsonian gait is characterised by a reduced arm swing, increased tremor of the upper extremity during walking, turning en bloc and slow, shuffling gait on a narrow base.[28,43] Patients may initiate walking with a series of rapid, short, shuffling steps prior to breaking into a normal stepping pattern (i.e., start hesitation).[28] Once walking is initiated, it may be interrupted by short shuffling steps or cessation of movement (i.e., freezing) if an obstacle is encountered.[28]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

BASAL GANGLIA

- Globus pallidus pars interna
- Globus pallidus pars externa
- Putamen
- Caudate nucleus
- Substantia nigra
- Subthalamic nuclei
- Striatum

CONDITION/S ASSOCIATED WITH[4,28,41,43,45]

Common

- Parkinson's disease
- Drugs – dopamine antagonists (e.g. haloperidol, metoclopramide)

Less common

- Lacunar infarction, basal ganglia
- Basal ganglia haemorrhage
- Multisystem atrophy
- Progressive supranuclear palsy
- Corticobasilar degeneration

MECHANISM/S

Postural changes in parkinsonism (e.g. stooped posture, shoulder flexion) move the patient's centre of gravity forward, worsening balance during locomotion. During initiation of movement, patients may take a series of small, rapid steps (i.e., festination) to accommodate for balance disequilibrium caused by the generalised flexion posture.[28] See also 'Bradykinesia' in this chapter.

Parkinsonian tremor

DESCRIPTION

The parkinsonian tremor is a 4- to 6-Hz 'pill-rolling' tremor of the fingertips, hand and forearm that is more pronounced at rest (i.e., a resting tremor).[4]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

BASAL GANGLIA

- Globus pallidus pars interna
- Globus pallidus pars externa
- Putamen
- Caudate nucleus
- Substantia nigra
- Subthalamic nuclei
- Striatum

CONDITION/S ASSOCIATED WITH[4,41]

Common

- Parkinson's disease
- Drugs – dopamine antagonists (e.g. haloperidol, metoclopramide)

Less common

- Lacunar infarction, basal ganglia
- Basal ganglia haemorrhage
- Multisystem atrophy
- Progressive supranuclear palsy
- Corticobasilar degeneration

MECHANISM/S

The mechanism of parkinsonian tremor is not known. Rhythmic and synchronous excitation of neurons in the subthalamic nucleus and globus pallidus pars interna correlates with tremor in the limbs of patients with Parkinson's disease and monkeys treated with MPTP.[44,166] The underlying pathophysiology may be due to one or more central pacemakers or circuits of oscillating neuronal activity in the basal ganglia.[167]

SIGN VALUE

Refer to Table 5.26 for clinical utility.

TABLE 5.26 Clinical utility of resting tremor in Parkinson's disease[166]

	Sensitivity	Specificity	Positive LR	Negative LR
Resting tremor[45]	76%	39%	NS	NS

Adapted from McGee S, *Evidence Based Physical Diagnosis*, 2nd edn, St. Louis: Saunders, 2007.

Photophobia

DESCRIPTION

Photophobia is light-induced ocular and/or cephalic discomfort.[168] The patient exhibits discomfort and aversion to light stimuli, resulting in involuntary eye closure and gaze deviation.

CONDITION/S ASSOCIATED WITH[168,169]

Common

- Migraine
- Corneal abrasion
- Contact lens acute red eye
- Viral meningitis
- Hyphaema

Less common

- Glaucoma
- Subarachnoid haemorrhage
- Meningitis (e.g. bacterial, viral, fungal, non-infectious)
- Anterior uveitis
- HSV keratitis

MECHANISM/S

The mechanism of photophobia is not known.[168,170] Photophobia may be a protective mechanism that protects the central retina from potentially damaging short wavelength visible light.[168,170]

Causes of photophobia include:

1. inflammation of the meninges
2. migraine
3. corneal injury
4. inflammation of the anterior chamber.

Inflammation of the meninges

Meningeal irritation is caused by infection, non-infectious inflammation, chemical inflammation and subarachnoid haemorrhage. Associated signs of meningism include nuchal rigidity, Kernig's sign, Brudzinski's sign and jolt sign.

Migraine

Non-image-forming retinal neuroepithelial cells project to an area in the posterior thalamus that also receives input from the dura mater. The cells in the posterior thalamus respond to input from both the non-image-forming retinal neuroepithelial cells and trigeminal and cervical nerves innervating the dura mater. In migraine, it has been suggested that input from the retinal neuroepithelial cells potentially augments migraine pain, resulting in photophobia.[170]

Corneal injury

Traumatic and inflammatory disorders of the cornea cause photophobia. The cornea is densely innervated, and light exacerbates ocular discomfort. Causes include contact lens acute red eye and corneal abrasion.

Inflammation of the anterior chamber

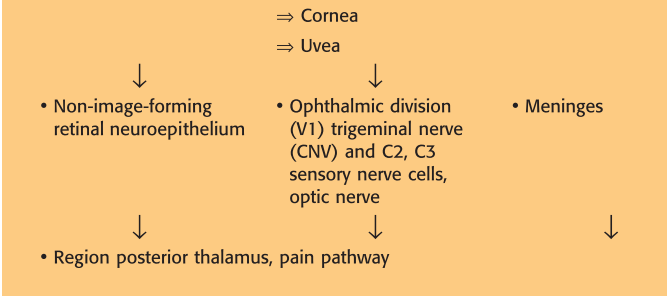
Inflammation or mechanical irritation of the iris, pupillary sphincter muscle and radial muscle cause photophobia. Discomfort is likely exacerbated by mechanical stress due to the change in pupil size during the pupillary light response and hippus.[169] Causes include anterior uveitis, acute angle closure glaucoma and hyphaema.[169]

SIGN VALUE

Photophobia is a sign of meningeal irritation, but is also associated with several other neurological and ocular disorders.

Photophobia occurs in more than 80% of patients with migraine.[169]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY



Physiological tremor

DESCRIPTION

Physiological tremor is a 7- to 12-Hz tremor that is typically seen in the outstretched arm (i.e., a postural tremor).[4,18,171] Physiological tremor occurs in all normal subjects, although it may not be visible to the naked eye. Enhanced physiological tremor (i.e., the tremor becomes more prominent) is caused by a provoking factor such as hyperthyroidism, hypoglycaemia, withdrawal states, anxiety or fear.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

→ Sympathetic nervous system

× Agonist and antagonist muscle groups

CONDITION/S ASSOCIATED WITH

Common

- Normal

Less common (i.e., enhanced physiological tremor)

- Hyperthyroidism
- Hypoglycaemia
- Withdrawal states
- Sympathomimetic agents
- Fatigue
- Anxiety
- Fear

MECHANISM/S

Physiological tremor is mechanical in origin and results from oscillation of agonist and antagonist muscle groups due to the combined effect of firing motor neurons, synchronisation of muscle spindle feedback and mechanical properties of the limbs.[171] Enhanced physiological tremor is caused by increases in circulating catecholamines (e.g. adrenaline, noradrenaline) and/or catecholamine receptor upregulation (e.g. hyperthyroidism), which increases the twitch force of motor units.[172]

SIGN VALUE

Uncomplicated physiological tremor has no clinical significance.[173] Enhanced physiological tremor may be associated with an underlying disorder (e.g. hyperthyroidism, sympathomimetic agent toxicity, withdrawal state).

Pinpoint pupils

DESCRIPTION

Pinpoint pupils are symmetric, constricted pupils with a diameter <2 mm.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

Central pathways

- Kappa-1 ($\otimes\kappa_1$) receptor
- Alpha-2 ($\otimes\alpha_2$) receptor

Sympathetic pathway

FIRST-ORDER NEURON

- Hypothalamus

↓

- Sympathetic fibres, brainstem

↓

- Sympathetic fibres, intermediate horn, spinal cord

↓

SECOND-ORDER NEURON (PREGANGLIONIC FIBRE)

- Sympathetic trunk

↓

- Superior cervical ganglion C2

↓

THIRD-ORDER NEURON (POSTGANGLIONIC FIBRE)

- Superior cervical ganglion C2

↓

- Ciliary body

↓

× Pupillary dilator muscles

Parasympathetic pathway

- Edinger–Westphal nucleus, midbrain

↓

- Oculomotor nerve (CNIII)

↓

- Ciliary ganglion

↓

- Short ciliary nerves

↓

- Neuromuscular junction

↓

× Pupillary constrictor muscle

⇒ Iris

CONDITION/S ASSOCIATED WITH[174–177]

Common

- Opioid toxicity (e.g. morphine, heroin)
- Senile miosis

Less common

- Pontine haemorrhage
- Cholinergic toxicity (e.g. organophosphate poisoning)
- Upward transtentorial herniation
- Clonidine toxicity
- Beta-adrenergic antagonist toxicity (e.g. carvedilol)

MECHANISM/S

The causes of pinpoint pupils are:

1. opioid toxicity
2. pontine haemorrhage
3. cholinergic toxicity
4. clonidine toxicity
5. cerebral herniation with pontine compression
6. beta-blocker toxicity
7. senile miosis in normal ageing.

Opioid toxicity

Binding of opioids at central kappa-1 (κ_1) receptors causes miosis.[174] Not all opioids cause pupillary constriction due to heterogenous binding affinity at κ_1 receptors. Patients taking meperidine, propoxyphene and pentazocine may not have pupillary constriction.[174,175]

Pontine haemorrhage

Pontine haemorrhage disrupts the descending sympathetic fibres in the pons, resulting in unopposed parasympathetic input and bilateral miosis.[176] Associated features include profound bilateral cranial nerve signs (e.g. facial nerve palsy, abducens nerve palsy), motor long tract signs, coma and cerebral herniation.

Cholinergic toxicity

Cholinergic toxicity causes bilateral miosis due to potentiation of muscarinic receptors at the neuromuscular junction. Muscarinic stimulation also results in diarrhoea, urination, bradycardia, bronchorrhoea, bronchospasm, excitation of skeletal muscle, lacrimation and gastrointestinal distress.[177] Causes of cholinergic toxicity include organophosphate and carbamate toxicity (e.g. insecticide poisoning).

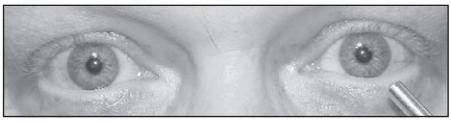


Figure 5.72 Bilateral pinpoint pupils, less than 2 mm in diameter and symmetric
Reproduced, with permission, from Curnyn KM, Kaufman LM, Pediatric Clinics of North America 2003; 50(1): 25–40, Fig 7a.

Clonidine toxicity

Clonidine is a central alpha-2 (α_2) receptor agonist that inhibits central sympathetic outflow. Inhibition of norepinephrine release causes decreased sympathetic outflow, resulting in bilateral miosis.[178–180]

Cerebral herniation with pontine compression

Central transtentorial herniation, cerebellotonsillar herniation and upward transtentorial herniation cause bilateral miosis due to compression of the pons.[117] Central transtentorial herniation is typically caused by an expanding vertex, frontal lobe or occipital lobe lesion.[117] Cerebellotonsillar herniation is most commonly caused by a cerebellar mass or rapid displacement of the brainstem.[117,181] Upward transtentorial herniation typically results from an expanding posterior fossa lesion.[117]

Beta-blocker toxicity

Beta-adrenergic antagonism relaxes the pupillary dilator muscle and results in miosis.

Senile miosis in normal ageing

With normal ageing, the pupils decrease in size and have a decreased mydriatic response in low light conditions.[182]

SIGN VALUE

Pinpoint pupils are a sign of several toxicological and neurological disorders. The most common cause of pinpoint pupils in patients with altered levels of consciousness, or coma, is opioid toxicity.

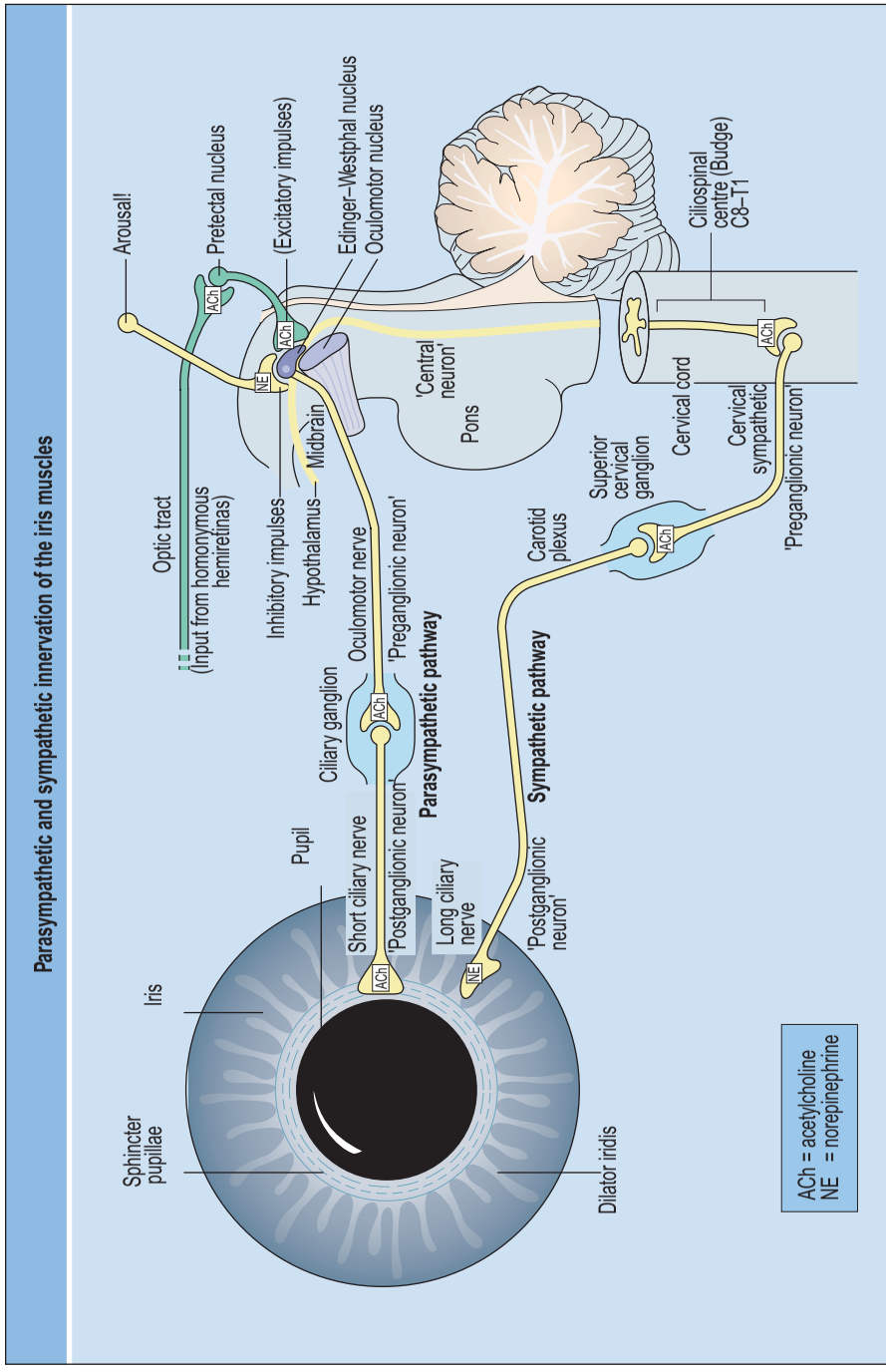


Figure 5.73 Parasympathetic and sympathetic pathways innervating the iris muscles

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 9-19-5.

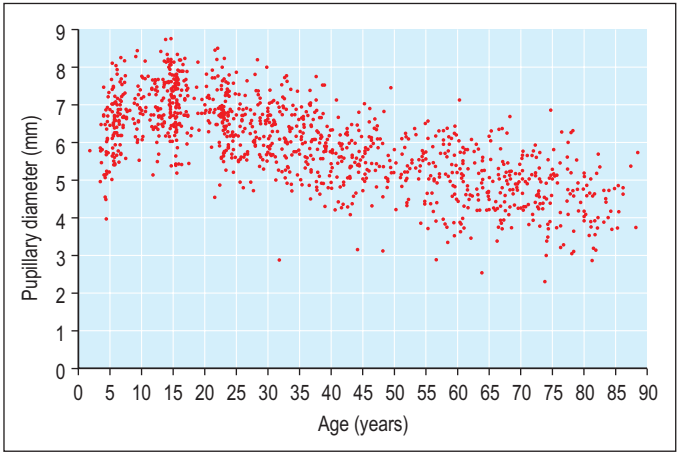


Figure 5.74 Changes in pupillary size (horizontal diameter) in darkness at various ages

Reproduced, with permission, from Dyck PJ, Thomas PK, *Peripheral Neuropathy*, 4th edn, Philadelphia: Saunders, 2005: Fig 9-5.

Pronator drift

DESCRIPTION

There is asymmetric downward arm movement when the patient extends both arms upright in the supinated position (e.g. palms straight up) with the eyes closed and is asked to hold them completely still. Downward arm drift, forearm pronation and flexion of the wrist and elbow typically begin distally and progress proximally.[18]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

UPPER MOTOR NEURON
- Motor cortex
↓
- Corona radiata, subcortical white matter
↓
- Posterior limb, internal capsule
↓
- Corticospinal tracts, medial brainstem
↓
∅ Pyramidal decussation, medulla
↓
- Lateral corticospinal tracts, spinal cord

CEREBELLUM
- Intermediate hemisphere
→ Lateral corticospinal tract
→ Rubrospinal tract
- Lateral hemisphere
→ Lateral corticospinal tract

PROPRIOCEPTION PATHWAY
⊗ Proprioceptive receptor
↓
- Peripheral nerve
↓
- Dorsal horn grey matter, spinal cord
↓
- Dorsal columns, spinal cord
↓
- Nucleus gracilis and nucleus cuneatus, medulla
↓
∅ Medial lemniscus, medulla
↓
- Medial lemniscus, brainstem

CONDITION/S ASSOCIATED WITH

Common
- Cerebral infarction
- Cerebral haemorrhage
- Cervical cord lesion

Less common
- Lacunar infarction, posterior limb internal capsule
- Multiple sclerosis
- Mass lesion (e.g. tumour, abscess, AVM)

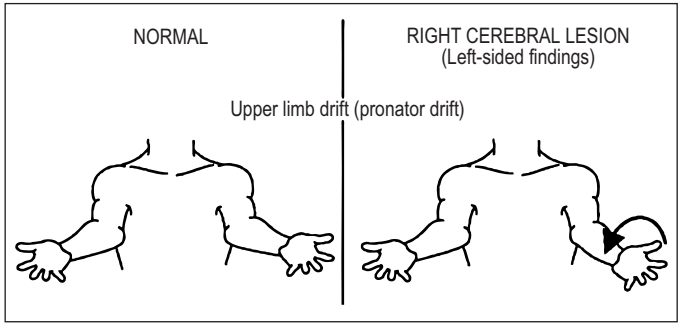


Figure 5.75 Pronator drift: the left arm drifts outward and rotates inward

Based on McGee S, *Evidence-Based Physical Diagnosis*, 2nd edn, Philadelphia: Saunders, 2007: Fig 57.1.

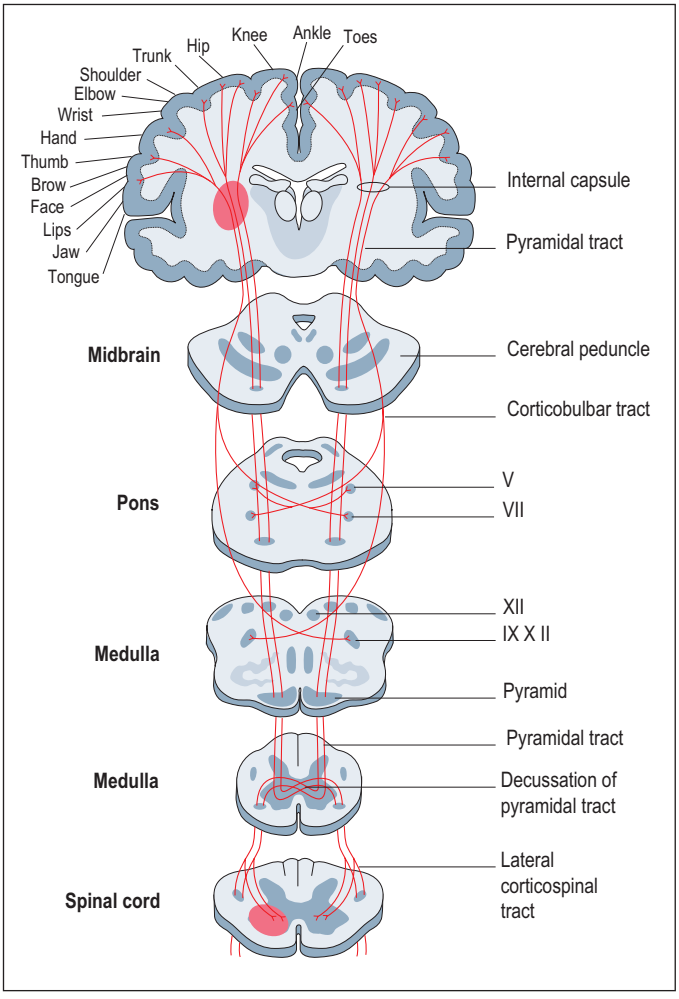


Figure 5.76 Upper motor neuron anatomy

Reproduced, with permission, from Clark RG, *Manter and Gatz's Essential Neuroanatomy and Neurophysiology*, 5th edn, Philadelphia: FA Davis Co, 1975.

TABLE 5.27 Clinical utility of pronator drift in unilateral cerebral hemisphere lesions

	Sensitivity	Specificity	Positive LR	Negative LR
Pronator drift[40,119]	79–92%	90–98%	10.3	0.1

Adapted from McGee S, *Evidence Based Physical Diagnosis*, 2nd edn, St. Louis: Saunders, 2007.

MECHANISM/S

When visual cues are removed, subtle upper motor neuron weakness causes the weak limb to drift downward.

SIGN VALUE

Pronator drift is a more sensitive test than power testing alone to detect upper motor neuron weakness.[4,18]

Refer to Table 5.27 for clinical utility.

Ptosis

DESCRIPTION

Ptosis is an abnormally droopy eyelid. It can be unilateral or bilateral. Normally, the upper eyelid covers the upper 1–2 mm of the iris, and the lower eyelid just touches the lower border of the iris.[7]

CONDITION/S ASSOCIATED WITH[7,183]

Common

- Horner's syndrome
- Oculomotor nerve (CNIII) palsy
- Levator aponeurosis dehiscence
- Dermatochalasis

Less common

- Myasthenia gravis
- Myotonic dystrophy
- Mitochondrial myopathy

MECHANISM/S

Causes of ptosis include:[7,184,185]

1. Horner's syndrome
2. oculomotor nerve (CNIII) palsy
3. disorders of the neuromuscular junction
4. myotonic dystrophy
5. mechanical disorders of the periorbital connective tissue.

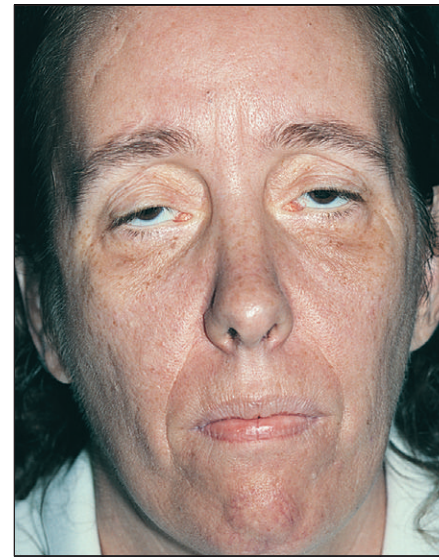


Figure 5.77 Patient with myotonic dystrophy with the characteristic 'hatchet facies' and bilateral ptosis

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 9-17-4.

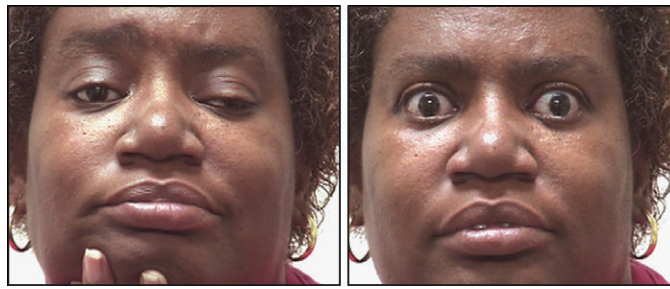


Figure 5.78 Patient with myasthenia gravis before and after the edrophonium test showing bilateral ptosis, more prominent on the left

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 82-4.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[7]

Superior tarsal muscle and sympathetic pathway

FIRST-ORDER NEURON

- Hypothalamus

↓

- Sympathetic fibres, brainstem

↓

- Sympathetic fibres, intermediate horn, spinal cord T1

↓

SECOND-ORDER NEURON (PREGANGLIONIC FIBRE)

- Sympathetic trunk

⇒ Lung apex

↓

- Superior cervical ganglion C2

↓

THIRD-ORDER NEURON (POSTGANGLIONIC FIBRE)

- Superior cervical ganglion C2

⇒ Carotid sheath

⇒ Carotid artery

⇒ Superior orbital fissure

⇒ Cavernous sinus

⇒ Orbital apex

↓

× Superior tarsal muscle

Levator palpebrae muscle and parasympathetic pathway

- Edinger–Westphal nucleus, midbrain

↓

- Oculomotor nerve (CNIII)

↓

- Posterior communicating artery, circle of Willis

⇒ Cavernous sinus

⇒ Superior orbital fissure, sphenoid bone

⇒ Orbital apex

↓

- Ciliary ganglion

↓

× Levator palpebrae muscle

Horner's syndrome

Horner's syndrome is caused by a lesion in the sympathetic pathway, which innervates the superior tarsal muscle (i.e., Müller's muscle), radial muscle of the iris and sweat glands in the face. Superior tarsal muscle weakness causes ptosis in Horner's syndrome. See 'Horner's syndrome' in this chapter.

Oculomotor nerve (CNIII) palsy

The levator palpebrae muscle is innervated by the parasympathetic fibres of the oculomotor nerve. Oculomotor nerve palsy results in ptosis due to weakness of the levator palpebrae muscle.[7] See 'Oculomotor nerve (CNIII) palsy' in this chapter.

Disorders of the neuromuscular junction

Myasthenia gravis is an autoimmune disorder characterised by antibodies against post-synaptic acetylcholine receptors of the neuromuscular junction. The extraocular muscles and facial muscles are predominantly affected. In myasthenia gravis, muscle weakness increases with use (i.e., fatiguability). In addition, muscle weakness may resolve if the temperature of the muscle is decreased, which can be demonstrated with the 'ice-on-eyes' test at the bedside.[185]

Myotonic dystrophy

Unlike most other primary disorders of muscle (i.e., myopathies), myotonic dystrophy causes weakness in the facial and peripheral muscle groups. Other features of myotonic dystrophy include percussion and grip myotonia.[183]

Mechanical disorders of the periorbital connective tissue

Levator aponeurosis dehiscence is caused by dissociation of the levator muscle and connective tissue from the tarsal insertion site. Focal swelling or degenerative changes in the skin and soft tissues of the eyelid can cause ptosis. Dermatochalasis is characterised by redundant tissue in the upper eyelid causing the upper lid to droop.

SIGN VALUE

Ptosis is a sign of eyelid muscle weakness or a disorder of the connective tissue of the eyelid.

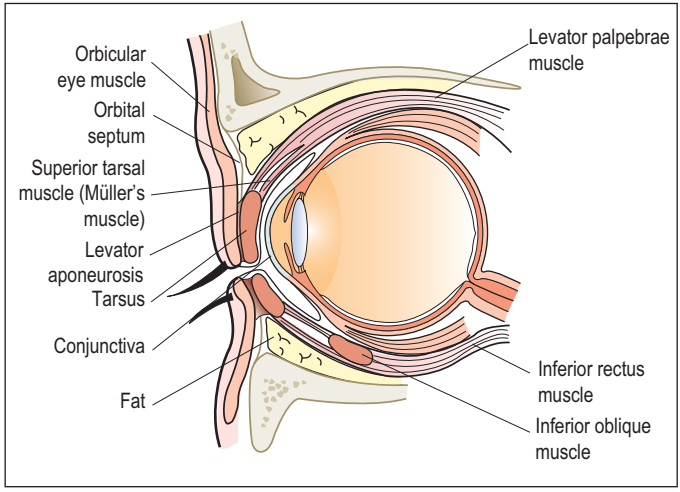


Figure 5.79 Anatomy of the eyelid muscles

Reproduced, with permission, from Flint PW et al, *Cummings Otolaryngology: Head and Neck Surgery*, 5th edn, Philadelphia: Mosby, 2010: Fig 30-9.

Relative afferent pupillary defect (RAPD) (Marcus Gunn pupil)

DESCRIPTION

Paradoxical dilation of both pupils occurs when the torch is moved from the normal eye to the abnormal eye (i.e., the eye with the afferent pupillary defect) during the swinging torch test.[4] An afferent pupillary defect is a disorder of the afferent limb of the pupillary light response pathway (e.g. optic nerve, retinal neuroepithelium).

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

AFFERENT LIMB
- Retinal neuroepithelium
- ↓
- Optic nerve (CNII)
- ↓
- Pretectal nucleus, midbrain
- ↓
- ↔ Bilateral innervation of Edinger–Westphal nuclei
- ↓

EFFERENT LIMB
- Edinger–Westphal nucleus, midbrain
- ↓
- Oculomotor nerve (CNIII)
- ↓
- Ciliary ganglion
- ↓
- Short ciliary nerves
- ↓
- × Pupillary constrictor muscle

CONDITION/S ASSOCIATED WITH[4,186]

Common

- Optic neuritis (e.g. multiple sclerosis)
- Anterior ischaemic optic neuropathy (AION)

Less common

- Vitreal haemorrhage
- Retinal detachment
- Retinoblastoma
- Mass lesion (e.g. tumour, abscess)

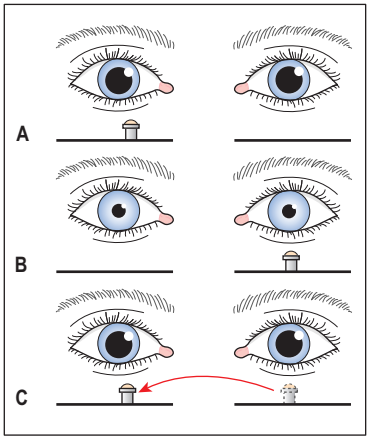


Figure 5.80 Schematic depiction of a right relative afferent pupillary defect identified using the swinging torch test

A, Right eye illuminated; poor direct and consensual reaction; **B**, excellent direct and consensual response with illumination of the left eye; **C**, light swung from left to right with redilatation of both pupils.

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 39-3.

MECHANISM/S

A relative afferent pupillary defect is caused by asymmetrical input to the Edinger–Westphal nuclei from the afferent limb structures (e.g. optic nerve, retinal neuroepithelium).[4,186] Symmetrical disorders (i.e., symmetric disease in both optic nerves) do not cause a relative afferent pupillary defect. The swinging torch test is only able to detect relative differences between the two afferent pathways. Mechanisms of RAPD include:

1. optic nerve disorders
2. retinal neuroepithelium disorders (rare).

Optic nerve disorders

Asymmetric disorders of the optic nerve are the most common cause of an afferent pupillary defect. The patient may have

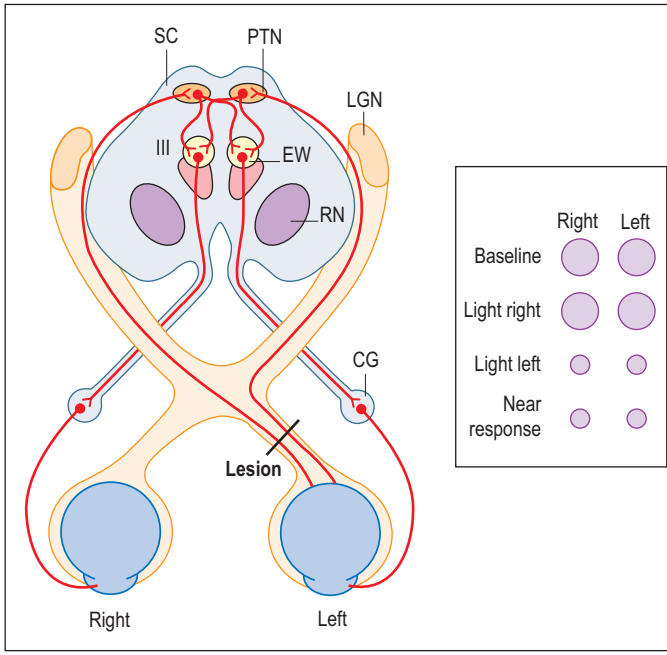


Figure 5.81 Pupillary response associated with RAPD

CG = ciliary ganglion; EW = Edinger–Westphal nucleus; LGN = lateral geniculate nucleus; PTN = pretectal nucleus; RN = red nucleus; SC = superior colliculus.

Reproduced, with permission, from Goldman L, Ausiello D, *Cecil Medicine*, 23rd edn, Philadelphia: Saunders, 2007: Fig 450-2.

associated clinical evidence of optic nerve dysfunction (e.g. papilloedema, decreased visual acuity, visual field defects, decreased colour vision).[158] Causes include optic neuritis, anterior ischaemic optic neuropathy (AION) and tumours of the optic nerve (e.g. optic nerve glioma). Idiopathic intracranial hypertension and other causes of elevated intracranial pressure may cause an RAPD if optic nerve dysfunction is asymmetrical.

Retinal neuroepithelium disorders (rare)

Severe asymmetric retinal disease is a less common cause of an afferent pupillary defect. Typically, the degree of paradoxical dilation is more subtle than in optic nerve dysfunction.[187,188] Causes include age-related macular degeneration, diabetic retinopathy, hypertensive retinopathy and central retinal artery occlusion.

SIGN VALUE

The sensitivity of an RAPD in the detection of unilateral optic nerve disease is 92–98%.[189,190]

Rigidity

DESCRIPTION

Rigidity is increased resistance to passive movement due to an abnormal increase in resting muscle tone. There are three defining characteristics:[4]

1. resistance independent of the velocity of muscle stretch (i.e., the magnitude of resistance during passive movement is the same with slow or fast movement)
2. equal flexor and extensor tone
3. no associated weakness.

Rigidity is a sign of extrapyramidal disease. It is sometimes referred to as plastic, waxy or lead-pipe rigidity.[6] Rigidity may worsen with active movements of the patient's contralateral limb, a phenomenon known as activated rigidity.[60]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

BASAL GANGLIA

- Globus pallidus pars interna
- Globus pallidus pars externa
- Putamen
- Caudate nucleus
- Substantia nigra
- Subthalamic nuclei
- Striatum

CONDITION/S ASSOCIATED WITH

Common

- Parkinson's disease
- Drugs – dopamine antagonists (e.g. haloperidol, metoclopramide)

Less common

- Diffuse white matter disease (e.g. lacunar infarction)
- Multisystem atrophy
- Progressive supranuclear palsy
- Corticobasilar degeneration

MECHANISM/S

The mechanism of rigidity in parkinsonism is not known.[44] Rigidity may result from changes in extrapyramidal regulation of supraspinal motor neurons and changes in spinal cord motor neuron activity in response to peripheral stimulation in stretch reflexes.[44] Cogwheel rigidity is a type of rigidity associated with Parkinson's disease in which rachet-like interruptions in muscle tone occur during passive range of motion.[60] Cogwheel rigidity has been attributed to the combined effects of rigidity and tremor.[60]

SIGN VALUE

Refer to Table 5.28 for clinical utility.

TABLE 5.28 Clinical utility of rigidity in Parkinson's disease

Prominent rigidity on initial examination in detecting Parkinson's disease[45]				
	Sensitivity	**Specificity**	**Positive LR**	**Negative LR**
Rigidity[45]	30%	43%	0.5	1.6

Adapted from McGee S, *Evidence Based Physical Diagnosis*, 2nd edn, St. Louis: Saunders, 2007.

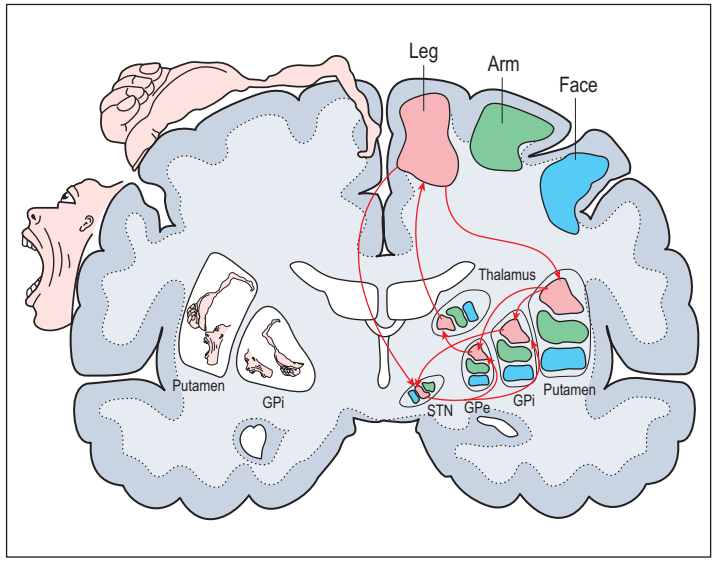


Figure 5.82 Basal ganglia motor circuit and somatotopic organisation

GPe = globus pallidus pars externa; GPi = globus pallidus pars interna; STN = subthalamic nucleus.

Reproduced, with permission, from Rodriguez-Oroz MC, Jahanshahi M, Krack P et al, Lancet Neurol 2009; 8: 1128–1139, Fig 2.

Romberg's test

DESCRIPTION

The patient is asked to stand with feet together, close both eyes and maintain the posture for 60 seconds. If the patient cannot stand for 60 seconds with feet together and eyes closed, the test is positive.[4]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

- Vestibular system
- Proprioceptive pathways
- Visual pathways

CONDITION/S ASSOCIATED WITH

Common

- Sensory peripheral neuropathy
- Vestibular neuritis
- Vestibulotoxic drugs (e.g. furosemide, gentamicin)

Less common

- Subacute combined degeneration of the cord (Vitamin B12 deficiency)
- Tabes dorsalis (e.g. tertiary syphilis)

MECHANISM/S

Three things maintain postural stability when standing: visual information, vestibular function and proprioception (refer to Table 5.29). Note that the majority of patients with cerebellar lesions are unable to maintain balance despite visual cues.[4,68] A positive Romberg test is caused by:

1. proprioceptive dysfunction
2. vestibular dysfunction.

Proprioceptive dysfunction

In patients with mild proprioceptive loss, visual cues may be sufficient to compensate for the deficit to maintain postural stability. Thus, when visual input is removed, compensation is no longer sufficient to maintain postural stability, resulting in a positive Romberg's test. Causes include sensory peripheral neuropathy and dorsal column dysfunction (e.g. tabes dorsalis, subacute combined degeneration of the cord).

Vestibular dysfunction

In patients with vestibular dysfunction (e.g. vestibular neuritis), visual cues may be sufficient to accommodate disequilibrium to maintain postural stability. When visual information is removed, vertigo and/or disequilibrium causes postural instability.

SIGN VALUE

In a study, 153 patients (115 control subjects of normal health, 13 patients with cerebellar ataxia and 25 patients with sensory ataxia) were assessed with the Romberg test (a positive test was defined as inability to stand for 60 seconds with feet together and eyes closed). All the healthy subjects had a negative result. Half of the patients with proprioceptive loss lasted only 10 seconds before having a positive test.[191]

TABLE 5.29 Functional anatomy of the cerebellum and associated motor pathways

Cerebellar anatomy	Function	Associated motor pathways
Vermis and flocculonodular lobe	• Proximal limb and trunk coordination • Vestibulo-ocular reflexes	• Anterior corticospinal tract • Reticulospinal tract • Vestibulospinal tract • Tectospinal tract

Adapted from Blumenfeld H, *Neuroanatomy Through Clinical Cases*, Sunderland: Sinauer, 2002.

Sensory level

DESCRIPTION

A sensory level is a spinal level at which there is an abrupt sensory loss.[121]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

Spinal cord

DORSAL COLUMN PATHWAY

- Dorsal columns
- ∅ Medial lemniscus, medulla

SPINOTHALAMIC TRACTS

- Spinothalamic tracts
- ∅ White ventral commissure, spinal cord

MOTOR

- Corticospinal tract
- Anterior horn grey matter

CONDITION/S ASSOCIATED WITH

Common

- Spinal cord injury
- Mass lesion (e.g. tumour, abscess, AVM)
- Multiple sclerosis

Less common

- Transverse myelitis
- Anterior cord syndrome
- Epidural abscess

MECHANISM/S

A spinal cord lesion results in sensory deficits at the level of, and below, the lesion. Sensory pathways above the lesion are not affected and, thus, sensation remains intact in the spinal levels above the lesion.

SIGN VALUE

Identification of a sensory level has potential localising value in spinal cord lesions.

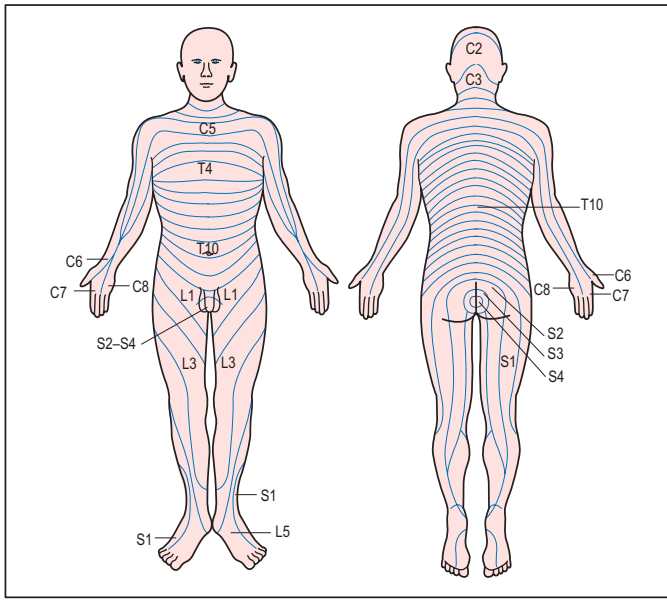


Figure 5.83
Dermatomes

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 30-3.

Sensory loss

DESCRIPTION

Sensory loss is characterised by the affected modalities (e.g. pain, temperature, light touch, vibration, proprioception) and anatomical distribution (see Table 5.30).

Light touch, vibration and proprioception

Light touch, vibration and proprioception sensation is predominantly mediated via the dorsal column–medial lemniscus pathway.

Pain and tempature

Pain and temperature sensation is mediated by the spinothalamic tract pathway.

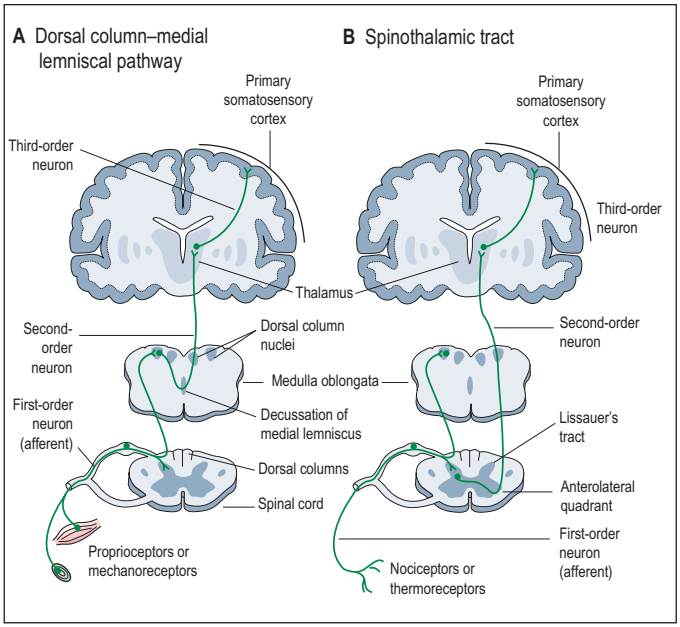


Figure 5.84 Relevant pathways in sensory loss

A Dorsal column–medial lemniscal, and **B** spinothalamic tract pathways.

Based on http://virtual.yosemite.cc.ca.us/rdroual/Course%20Materials/Physiology%20101/Chapter%20Notes/Fall%202007/chapter_10%20Fall%202007.htm [5 Apr 2011].

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[4,6]

DORSAL COLUMN AND MEDIAL LEMNISCUS PATHWAY (LIGHT TOUCH, VIBRATION AND PROPRIOCEPTION)

- Sensory cortex
↓
- Anterior limb, internal capsule
↓
- Ventral posterior lateral nuclei, thalamus
↓
- Medial lemniscus, brainstem
↓
∅ Medial lemniscus, medulla
↓
- Nucleus gracilis and nucleus cuneatus, medulla
↓
- Dorsal columns, spinal cord
↓
- Dorsal horn grey matter, spinal cord
↓
- Nerve root
⇒ Intervertebral disc
⇒ Intervertebral foramina
↓
- Peripheral nerve
⇒ Potential sites of nerve compression (e.g. carpal tunnel)
↓
⊗ Various sensory receptors

SPINOTHALAMIC TRACT (PAIN AND TEMPERATURE)

- Sensory cortex
↓
- Anterior limb internal, capsule
↓
- Ventral posterior lateral nuclei, thalamus
↓
- Spinothalamic tract, brainstem
↓
- Spinothalamic tract, spinal cord
↓
∅ Ventral white commissure (anterior commissure)
⇒ Central canal, spinal cord
↓
- Posterior horn grey matter
↓
- Posterior nerve root
⇒ Intervertebral disc
⇒ Intervertebral foramen
↓
- Peripheral nerve
⇒ Potential sites of nerve entrapment (e.g. carpal tunnel)
↓
⊗ Nociceptor, temperature receptor

CONDITION/S ASSOCIATED WITH

Common

- Compression mononeuropathy (e.g. carpal tunnel syndrome)
- Peripheral neuropathy (e.g. diabetic neuropathy)
- Cerebral infarction
- Cerebral haemorrhage
- Spinal cord injury
- Radiculopathy

Less common

- Transverse myelitis
- Lateral medullary syndrome (Wallenberg's syndrome)
- Compartment syndrome
- Syringomyelia
- Mass lesion (e.g. tumour, abscess)

MECHANISM/S

Causes of sensory loss include:

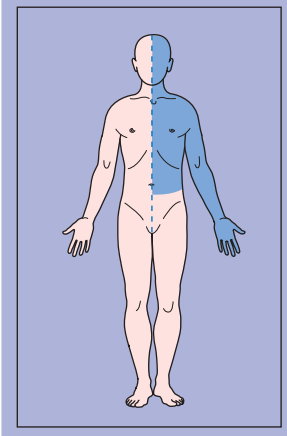
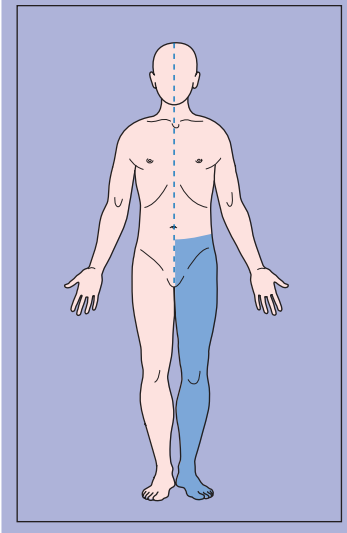
1. sensory cortex lesion
2. anterior limb of the internal capsule lesion
3. thalamus lesion
4. brainstem lesion
5. spinal cord lesion
6. radiculopathy
7. peripheral neuropathy.

Sensory cortex lesion

Unilateral lesions of the sensory cortex cause contralateral hemisensory loss in the distribution of structures of the sensory homunculus. Isolated lesions of the post-central gyrus may result in more sensory loss than motor loss.[121]

Text continued on page 396.

TABLE 5.30 Mechanisms of patterns of sensory loss

Pattern of sensory loss	Mechanism(s)
Face and arm  **FIGURE 5.85**	• MCA territory infarction • Mass lesion, sensory cortex
Leg  **FIGURE 5.86**	• Ipsilateral lumbar radiculopathy • Mass lesion, sensory cortex • ACA territory infarction • Ipsilateral spinal cord lesion below T1, above L1/L2

Continued

TABLE 5.30 Mechanisms of patterns of sensory loss—cont'd

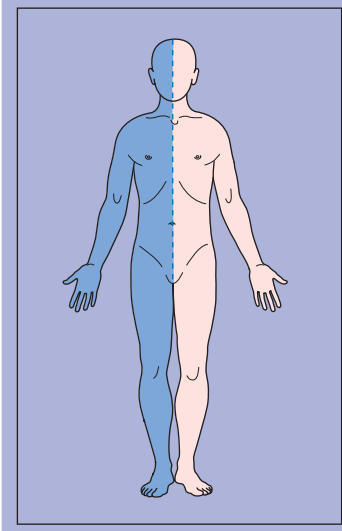
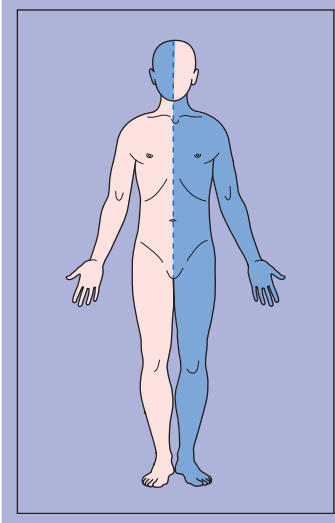
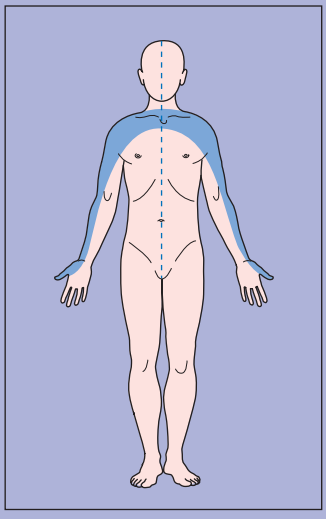
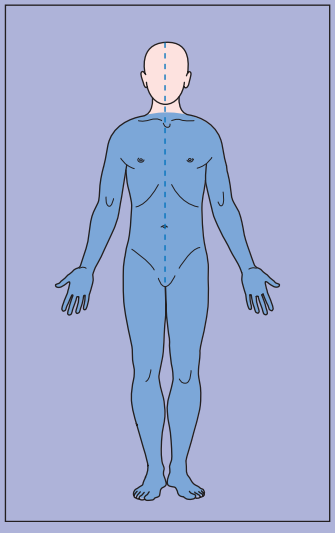
Pattern of sensory loss	Mechanism(s)
Face, arm, leg  **FIGURE 5.87**	• Thalamic lesion • Anterior limb, internal capsule lesion • ICA (ACA + MCA) territory infarction
Ipsilateral face + contralateral arm and leg  **FIGURE 5.88**	• Lateral medullary syndrome (Wallenberg's syndrome)

TABLE 5.30 Mechanisms of patterns of sensory loss—cont'd

Pattern of sensory loss	Mechanism(s)
Loss of pain and temperature in both arms in cape distribution  **FIGURE 5.89**	• Central cord syndrome, cervical spinal cord
Upper and lower limbs  **FIGURE 5.90**	• Cervical spinal cord lesion

Continued

TABLE 5.30 Mechanisms of patterns of sensory loss—cont'd

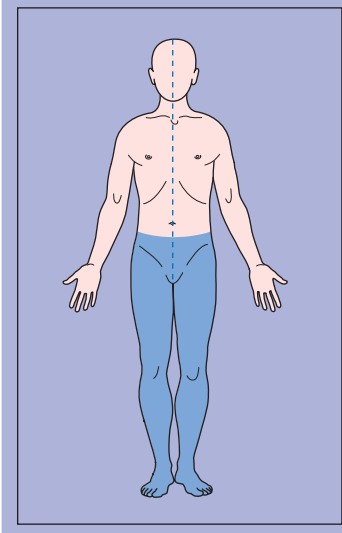
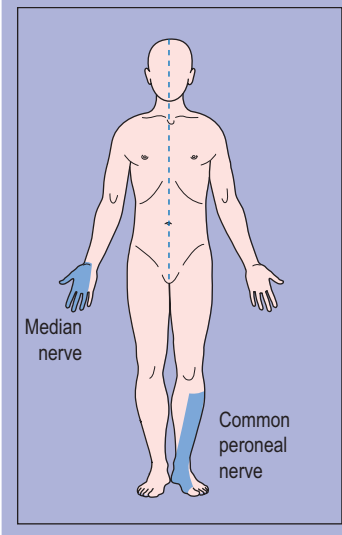
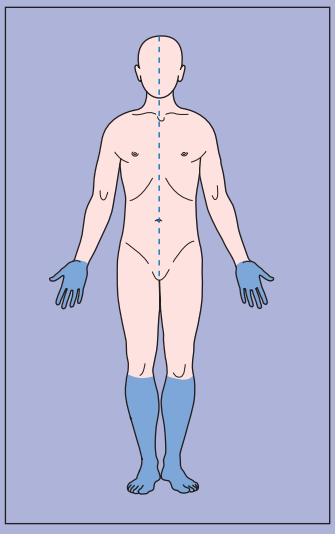
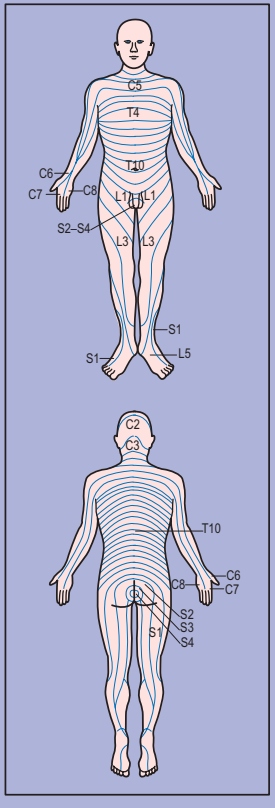
Pattern of sensory loss	Mechanism(s)
Lower limbs  **FIGURE 5.91**	• Spinal cord lesion below T1, above L1/L2
Peripheral nerve distribution  **FIGURE 5.92**	• Compression peripheral mononeuropathy

TABLE 5.30 Mechanisms of patterns of sensory loss—cont'd

Pattern of sensory loss	Mechanism(s)
Glove-and-stocking distribution  **FIGURE 5.93**	• Length-dependent peripheral neuropathy
Dermatomal distribution  **FIGURE 5.94**	• Radiculopathy

Anterior limb, internal capsule lesion

A lesion in the anterior limb of the internal capsule typically causes pure contralateral hemisensory loss of the face, arm and leg due to the dense distribution of sensory fibres in this region.[121] Muscle weakness may coexist if there is involvement of the posterior limb of the internal capsule. The most common cause is a lacunar infarction.

Thalamus lesion

The most common cause of pure hemisensory loss in the absence of motor findings is thalamic infarction.[121] Causes of thalamic lesions include lacunar infarction, cerebral haemorrhage and tumours.

Brainstem lesion

Brainstem lesions are characterised by crossed motor sensory and/or motor deficits. Cranial nerve nuclei dysfunction causes ipsilateral cranial nerve abnormalities. Long tract dysfunction (e.g. pyramidal tracts, medial lemniscus, spinothalamic tract) results in contralateral motor and sensory abnormalities below the lesion. The prototypical brainstem syndrome with crossed sensory findings is Wallenberg's syndrome. See also 'Wallenberg's syndrome' in this chapter.

Spinal cord lesion

Spinal cord lesions cause ipsilateral loss of light touch, vibration and proprioception sensation because the dorsal column pathway decussates in the medulla (above the lesion). Contralateral loss of pain and temperature sensation results because the spinothalamic tract decussates at each spinal level (below the lesion). There will also be a narrow band of complete sensory loss at the level of the lesion. A sensory level (i.e., a discrete loss of sensation below a certain dermatomal level) is characteristic.

Radiculopathy

Disorders of the nerve root typically cause positive (e.g. pain) and negative (e.g. hypoalgesia, analgesia) sensory findings in the distribution of the affected nerve root (i.e., dermatome). Sensory abnormalities typically occur prior to motor abnormalities. The most common causes are intervertebral disc disease and spondylosis (see Table 5.30).

Peripheral neuropathy

The most common mechanisms of peripheral neuropathy are: 1) length-dependent peripheral neuropathy and 2) compression mononeuropathy.

LENGTH-DEPENDENT PERIPHERAL NEUROPATHY

Length-dependent peripheral neuropathy is caused by axonal degeneration in the most distal portion of the nerve and progresses towards the cell body.[3,121] Causes of length-dependent peripheral neuropathy include diabetes mellitus, alcohol and inherited neuropathies.

COMPRESSION MONONEUROPATHY

Compression peripheral neuropathy is caused by mechanical injury that leads to degeneration of the axons and myelin distal to the site of injury (i.e., Wallerian degeneration). Motor and sensory deficits in the distribution of the affected peripheral nerve are characteristic.[3] Peripheral nerves susceptible to compression or traumatic injury are most commonly affected (e.g. median nerve, common peroneal nerve).

SIGN VALUE

The modality, or modalities, of sensory loss and anatomical distribution are important when considering the aetiologies of sensory loss.

Spasticity

DESCRIPTION

Spasticity is increased resistance to passive movement due to an abnormal increase in resting muscle tone. There are three distinct features:[4,192]

1. Resistance is velocity-dependent (i.e., muscle tone increases with the velocity of passive movement).
2. There is flexor–extensor tone dissociation (i.e., increased tone in flexors of the arms and extensors of the lower limbs).
3. Weakness is present.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

UPPER MOTOR NEURON

- Motor cortex

↓

- Corona radiata, subcortical white matter

↓

- Posterior limb, internal capsule

↓

- Corticospinal tracts, medial brainstem

↓

∅ Pyramidal decussation, medulla

↓

- Lateral corticospinal tracts, spinal cord

↓

MONOSYNAPTIC STRETCH REFLEX

→ Inhibitory interneuron
→ Sensory afferent neuron
→ Alpha motor neuron

CONDITION/S ASSOCIATED WITH

Common

- Cerebral infarction
- Cerebral haemorrhage
- Lacunar infarction, posterior limb internal capsule
- Multiple sclerosis

Less common

- Spinal cord injury
- Mass lesion (e.g. tumour, abscess, AVM)
- Progressive spastic paresis
- *Clostridium tetani*
- Strychnine

MECHANISM/S

Spasticity is caused by:

1. upper motor neuron disorder
2. toxicological and infectious disorders (rare).

Upper motor neuron disorder

Upper motor neuron dysfunction causes a decrease in inhibitory interneuron activity and an increase in gamma motor neuron activity, resulting in a state of hyperexcitability of alpha motor neurons.[57] Hyperexcitability of alpha neurons results in increased resting muscle tone and increased resistance during passive movement. In the hyperacute period following upper motor neuron injury, spasticity is often absent. It takes days to weeks for spasticity to develop following acute upper motor neuron injury.[39]

Toxicological and infectious disorders

Clostridium tetani produces a toxin that inhibits the release of GABA from inhibitory interneurons in the spinal cord, causing prolonged excitation of the alpha motor neuron, resulting in spastic paresis.[193] Strychnine blocks the uptake of glycine at post-synaptic spinal cord motor neurons, causing prolonged excitation of the alpha motor neuron and spastic paresis.[194]

SIGN VALUE

Spasticity is most commonly an upper motor neuron sign.

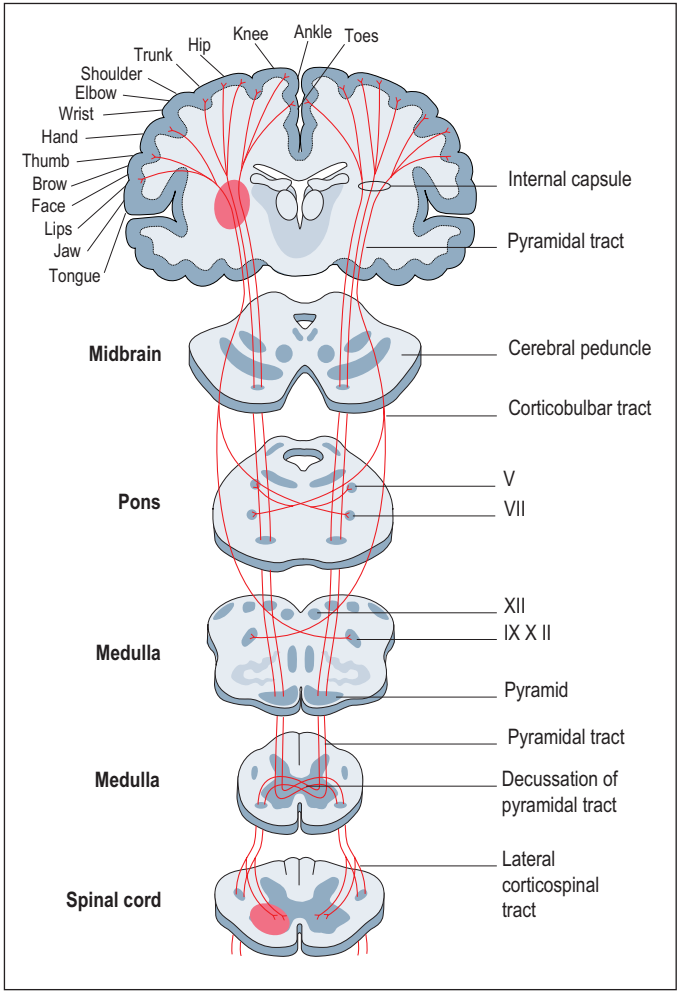


Figure 5.95 Upper motor neuron anatomy

Based on Clark RG, *Manter and Gatz's Essential Neuroanatomy and Neurophysiology*, 5th edn, Philadelphia: FA Davis Co, 1975.

Sternocleidomastoid and trapezius muscle weakness (accessory nerve [CNXI] palsy)

DESCRIPTION

Accessory nerve (CNXI) palsy results in sternocleidomastoid and/or trapezius muscle weakness.

Sternocleidomastoid weakness is elicited by resistance testing against head turning.

- Weakness head turn left → right sternocleidomastoid weakness
- Weakness head turn right → left sternocleidomastoid weakness

Trapezius weakness is elicited by resistance testing against shoulder shrugging. The levator scapulae muscle also plays a role in this movement.[6,195]

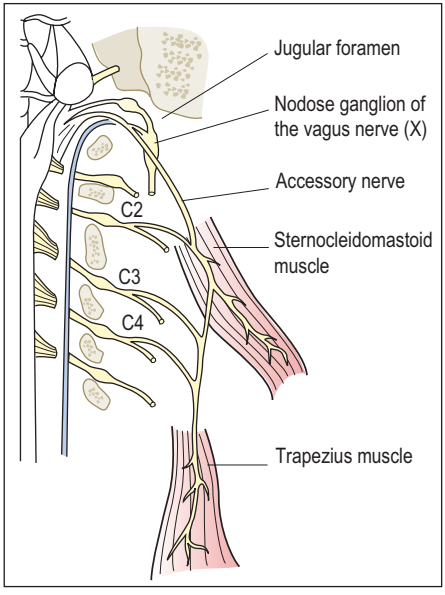


Figure 5.96 Innervation of the sternocleidomastoid and trapezius muscles by the accessory nerve (CNXI)

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 74-13.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

UPPER MOTOR NEURON
- Motor cortex

↓
- Corona radiata, subcortical white matter

↓
- Posterior limb, internal capsule

↓
- Pyramidal tracts, brainstem

↓
∅ Decussation 1

↓
∅ Decussation 2

↓
LOWER MOTOR NEURON
- Accessory nucleus, medulla

↓
- Accessory nerve

⇒ Foramen magnum

⇒ Posterior triangle, neck

↓
× Sternocleidomastoid muscle

CONDITION/S ASSOCIATED WITH

Common

- Iatrogenic (e.g. complication of neck dissection)
- Penetrating trauma posterior triangle neck

Less common

- Mass lesion (e.g. tumour, abscess)

MECHANISM/S

Accessory nerve palsy is most commonly caused by peripheral nerve lesions secondary to trauma or mass lesions. Accessory nerve palsies may spare the sternocleidomastoid muscle because its branches diverge early from the main nerve trunk.[196]

Tongue deviation (hypoglossal nerve [CNXII] palsy)

DESCRIPTION

The tongue deviates towards the side of the lesion.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

UPPER MOTOR NEURON
- Motor cortex

↓
- Corona radiata, subcortical white matter

↓
- Posterior limb, internal capsule

↓
- Pyramidal tracts, brainstem

↓

∅ Decussation

↓

LOWER MOTOR NEURON
- Hypoglossal nucleus, medulla

↓
- Hypoglossal nerve

⇒ Hypoglossal canal

⇒ Carotid artery

↓

× Genioglossus muscle

CONDITION/S ASSOCIATED WITH

Common

- Iatrogenic (e.g. complication of carotid endarterectomy)
- Penetrating neck trauma

Less common

- Carotid artery aneurysm
- Mass lesion (e.g. tumour, abscess)
- Carotid artery dissection

MECHANISM/S

The genioglossus muscle is innervated by the ipsilateral hypoglossal nerve and moves the tongue medially and forward. Normally, the medial forces of each genioglossus muscle are balanced and the tongue is protruded in the midline. If genioglossus weakness is present, the tongue deviates towards the side of weakness, due to loss of the medial force on the affected side.[4,6,197]

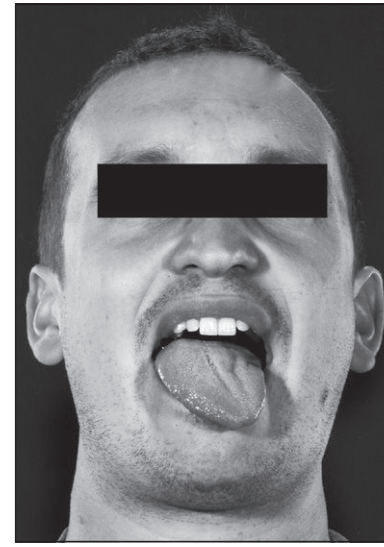


Figure 5.97 Patient with left hypoglossal nerve palsy with tongue deviation toward the side of the lesion

Reproduced, with permission, from Zafeiriou DI, N Engl J Med 2004; 350: e4.

Tongue deviation is caused by:
1. hypoglossal nerve palsy
2. medial medullary syndrome.

Hypoglossal nerve (CNXII) palsy

Hypoglossal nerve palsies are often accompanied by other cranial nerve findings.[198] Causes include hypoglossal canal stenosis, internal carotid artery aneurysm, internal carotid artery dissection, iatrogenic injury following carotid endarterectomy and penetrating neck injury.[199–201]

Medial medullary syndrome

Branch vertebral and/or anterior spinal artery territory infarction may result in lesions of the pyramidal tract, medial lemniscus and hypoglossal nuclei and fascicles.[6] This results in ipsilateral genioglossus weakness, contralateral arm and leg weakness, and contralateral decreased position and vibration sense.[6]

SIGN VALUE

The hypoglossal nerve is the most common cause of tongue deviation. The tongue deviates towards the side of the lesion.

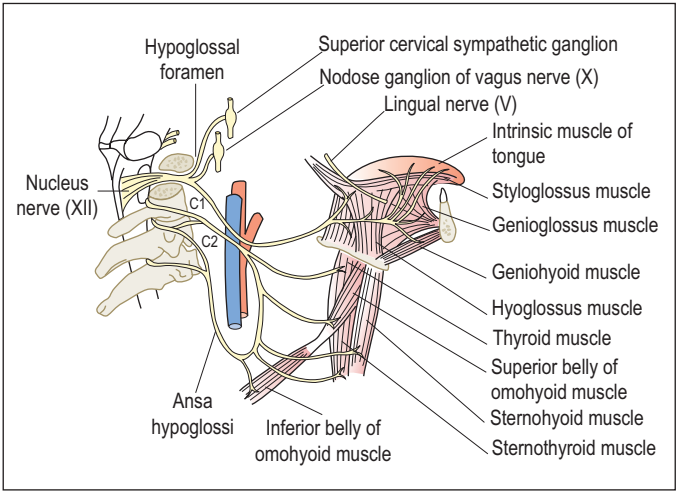


Figure 5.98
Neuroanatomy and topographical anatomy of the hypoglossal nerve (CNXII)

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 74-16.

Trochlear nerve (CNIV) palsy

DESCRIPTION

Trochlear nerve (CNIV) palsy is characterised by (findings in the primary gaze position):[1]

1. hypertropia (upward deviation)
2. extorsion (external rotation)
3. head tilt, in the direction opposite to the side of the affected eye.

Dysconjugate gaze worsens when the patient looks down and away from the side of the affected eye (such as when going down a spiral staircase).

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

- Trochlear nuclei, dorsal midbrain
- ↓
- ∅ Decussation
- ↓
- Trochlear nerve
- ⇒ Subarachnoid space
- ⇒ Superior orbital fissure
- ⇒ Cavernous sinus
- ⇒ Orbital apex
- ↓
- × Superior oblique muscle

CONDITION/S ASSOCIATED WITH[1,202–204]

Common

- Blunt head trauma
- Diabetic mononeuropathy/ microvascular infarction

Less common

- Cavernous sinus syndrome
- Midbrain lesion (e.g. tumour, multiple sclerosis)
- Hydrocephalus
- Pinealoma

MECHANISM/S

The trochlear nerve (CNIV) innervates the contralateral superior oblique muscle and decussates immediately after exiting the dorsal midbrain. Lesions of the trochlear nerve result in contralateral findings. The mechanisms of features of trochlear nerve palsy are described in Table 5.31.

The most common causes of isolated trochlear nerve palsy are traumatic injury and ischaemic microvascular disease.[1] The trochlear nerve is particularly vulnerable to traumatic injury due to its long course outside the brainstem.[1,204] Causes of trochlear nerve (CNIV) palsy include:

1. brainstem lesion
2. traumatic peripheral nerve injury
3. disorders of the subarachnoid space
4. cavernous sinus syndrome
5. orbital apex syndrome.

Brainstem lesion

Lesions of the trochlear nuclei cause contralateral superior oblique muscle paresis due to the decussation of the nerve as it exits the dorsal midbrain. Isolated trochlear nerve lesions in the brainstem are rare. Typically, in brainstem lesions, multiple brainstem localising findings will be present.[202,203]

TABLE 5.31 Mechanisms of features of trochlear nerve (CNIV) palsy

Feature of trochlear nerve palsy	Mechanism
• Hypertropia	→ Unopposed inferior oblique and superior rectus muscles.
• Extorsion	→ Unopposed inferior oblique muscle
• Head tilt	→ Patient accommodates extorted eye
• Impaired depression	→ Superior oblique weakness
• Impaired intorsion	→ Inferior oblique weakness

Figure 5.99 Patient with trochlear nerve (CNIV) palsy

A, Primary position with left hypertropia and extorsion; **B,** relatively normal left gaze away from fields of action of left superior orbital oblique muscle; **C**, right gaze; **D**, no vertical deviation of the left eye during contralateral head tilt, due to reflex excyclotorsion accomplished by the inferior rectus and inferior oblique muscles; **E**, pronounced left hypertropia on ipsilateral head tilt, following reflex incyclotorsion recruitment of superior rectus muscle and weak superior oblique muscle (due to inability to compensate superior rectus muscle contraction by the weak superior oblique muscle).

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn. St Louis: Mosby, 2008: Fig 11-10-4.

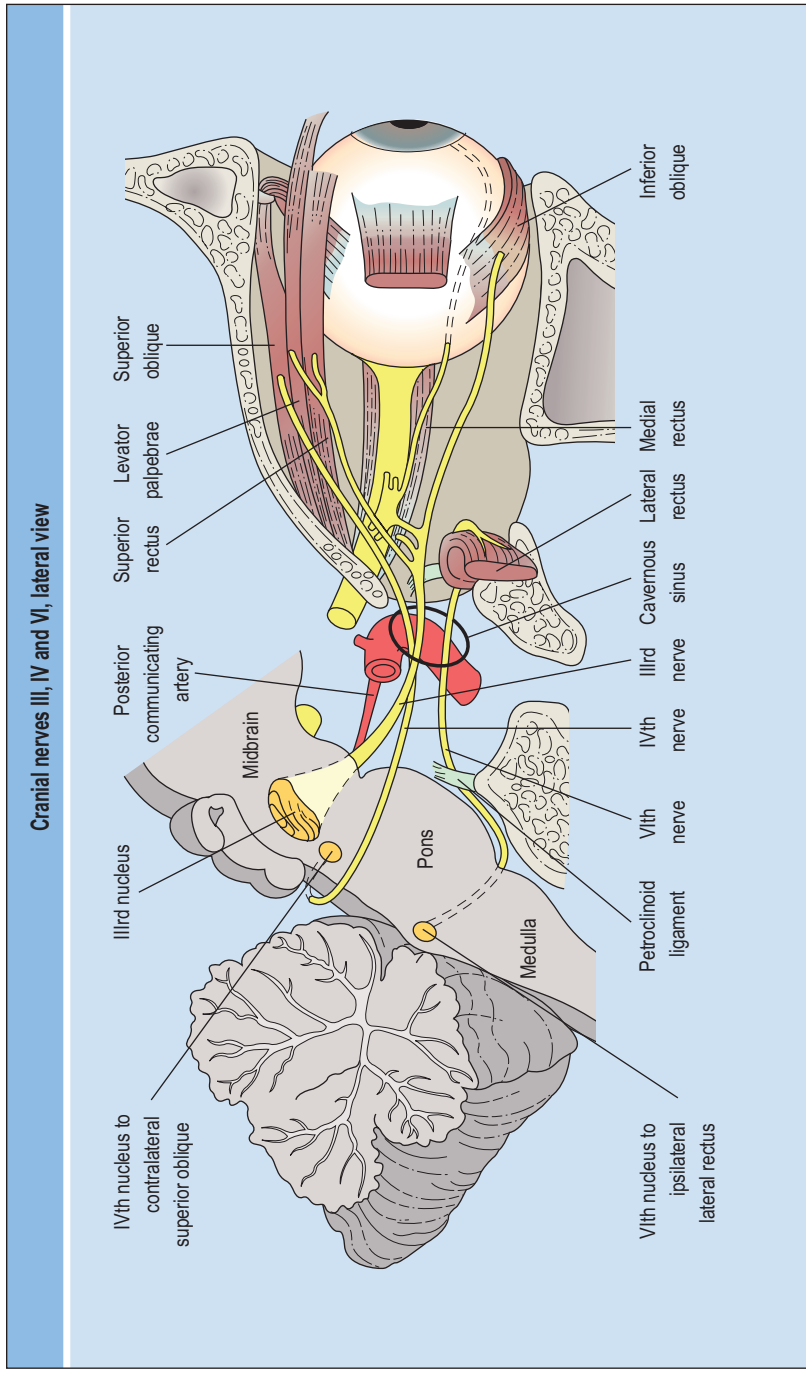


Figure 5.100 Lateral view of the trochlear nerve (CNIV)

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 9-15-1.

Traumatic peripheral nerve injury

Unlike other traumatic cranial neuropathies, which typically occur secondary to severe mechanisms of head injury, traumatic trochlear nerve injury may result from relatively minor trauma.[204] The trochlear nerve undertakes a long course after exiting the brainstem and is vulnerable to compression due to changes in pressure gradients in cerebral tissue caused by blunt head trauma.

Disorders of the subarachnoid space

Mass lesions may compress the trochlear nerve (CNIV) as it exits the brainstem and traverses the subarachnoid space. Causes include infectious or neoplastic meningeal irritation and trochlear nerve schwannoma.[203]

Cavernous sinus syndrome

See 'Cavernous sinus syndrome' in this chapter.

Orbital apex syndrome

See 'Orbital apex syndrome' in this chapter.

SIGN VALUE

In a study of patients with trochlear nerve palsy, approximately 45% of patients tilted their heads away from the side of the lesion.[205–207] When the patients tilted their heads towards the side of the lesion, 96% of patients experienced worsening in diplopia and hypertropia.[205,207]

Truncal ataxia

DESCRIPTION

Truncal ataxia is truncal postural instability while sitting upright and oscillatory movements of the head and trunk (i.e., titubation).[68] Patients may require assistance to maintain an upright posture.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

CEREBELLUM
- Vermis and flocculonodular lobe
  → Anterior corticospinal tract
  → Reticulospinal tract
  → Vestibulospinal tract
  → Tectospinal tract

CONDITION/S ASSOCIATED WITH[6,68]

Common

- Cerebellar infarction
- Cerebellar haemorrhage
- Alcohol
- Drugs (e.g. benzodiazepine, lithium, phenytoin)

Less common

- Multiple sclerosis
- Mass lesion (e.g. tumour, abscess, AVM)
- Arnold–Chiari malformation
- Paraneoplastic cerebellar degeneration

MECHANISM/S

Midline structures of the cerebellum (e.g. vermis and flocculonodular lobe) coordinate movements in the axial musculature via the descending axial motor pathways[6,68] Lesions in these structures cause truncal ataxia and titubation. Refer to Table 5.32 for motor pathways associated with the cerebellum.

SIGN VALUE

Truncal ataxia is a midline cerebellar sign.

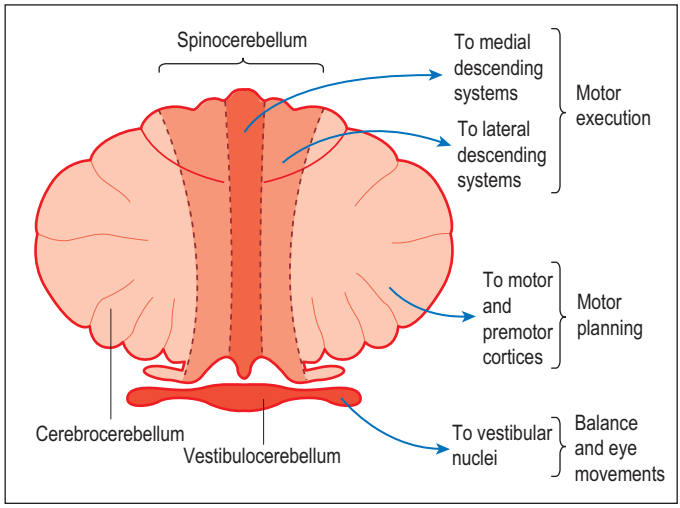


Figure 5.101 Functional anatomy of the cerebellum

Reproduced, with permission, from Barrett KE, Barman SM, Boitano S et al. *Ganong's Review of Medical Physiology*, 23rd edn. Available: http://accessmedicine.com [9 Dec 2010].

TABLE 5.32 Functional anatomy of the cerebellum and associated motor pathways

Cerebellar anatomy	Function	Associated motor pathways
Vermis and flocculonodular lobe	• Proximal limb and trunk coordination • Vestibulo-ocular reflexes	• Anterior corticospinal tract • Reticulospinal tract • Vestibulospinal tract • Tectospinal tract
Intermediate hemisphere	• Distal limb coordination	• Lateral corticospinal tracts • Rubrospinal tracts
Lateral hemisphere	• Motor planning, distal extremities	• Lateral corticospinal tracts

Adapted from Blumenfeld H, *Neuroanatomy Through Clinical Cases*, Sunderland: Sinauer, 2002.

Uvular deviation

DESCRIPTION

Dynamic deviation of the uvula to one side upon contraction of the palatal constrictor muscle. (*Note*: this does not include fixed uvular deviation, as seen in peritonsillar abscess.)

CONDITION/S ASSOCIATED WITH[1]

Common

- Diabetic mononeuropathy/ microvascular infarction
- Iatrogenic (e.g. complication of tonsillectomy)

Less common

- Lateral medullary syndrome (Wallenberg's syndrome)
- Cerebellopontine tumour
- Internal carotid artery dissection
- Glomus tumour

MECHANISM/S

Uvular deviation is caused by:

1. nucleus ambiguus lesion
2. vagus nerve (CNX) palsy.

Nucleus ambiguus lesion

A lesion of the nucleus ambiguus causes ipsilateral weakness of the palatal constictor muscles, and results in uvular

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[1]

UPPER MOTOR NEURON

- Motor cortex

↓

- Corona radiata, subcortical white matter

↓

- Posterior limb, internal capsule

↓

- Motor long tracts, brainstem

↓

∅ Decussation

↓

VAGUS NERVE

- Nucleus ambiguus and dorsal motor nucleus, medulla

⇒ Jugular foramen

↓

- Nodose ganglion

↓

× Palatal constrictors and intrinsic laryngeal muscles

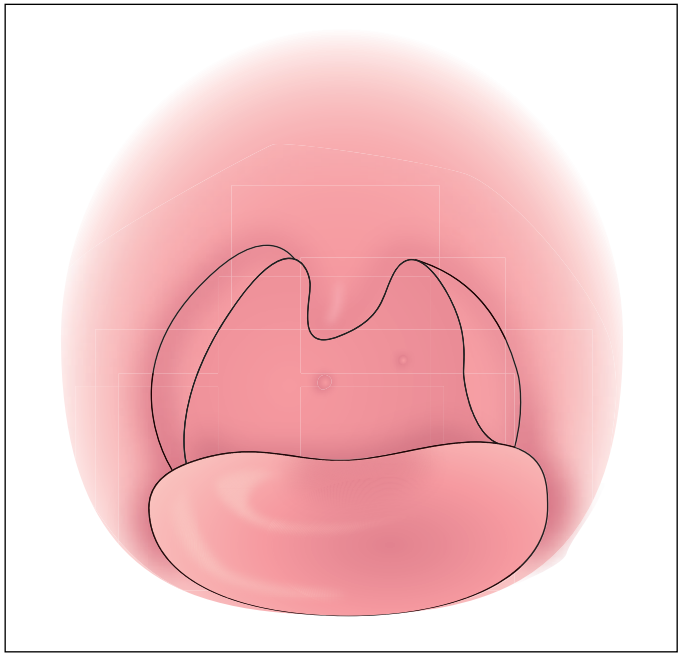


Figure 5.102 Uvular deviation to the right following acute stroke affecting the left glossopharyngeal nerve (CNIX)

Based on Scollard DM, Skinsnes OK, Oral Surg, Oral Med, Oral Pathol, Oral Radiol, Endodontol 1999; 87(4): 463–470.

deviation away from the side of the lesion. Causes include lateral medullary syndrome (Wallenberg's syndrome), abscess and multiple sclerosis.[1]

Vagus nerve (CNX) palsy

In vagus nerve palsy, ipsilateral weakness of the uvula and soft palate causes the uvula to deviate away from the affected side. Associated features include unilateral loss of pharyngeal and laryngeal sensation, unilateral loss of sensation in the external ear, dysphagia and hoarseness.[1] Causes include trauma, cerebellopontine angle tumours, iatrogenic and glomus tumour.

SIGN VALUE

Dynamic uvular deviation is a sign of vagus nerve (CNX) palsy or a nucleus ambiguus lesion.

Vertical gaze palsy

DESCRIPTION

Vertical gaze palsy is a group of uncommon gaze disorders that include upward gaze palsy, downward gaze palsy and a combined upward and downward gaze palsy.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY[138]

HIGHER CENTRE INPUT
- Cerebral hemisphere
- Superior colliculus
- Vestibular nuclei
- Cerebellum

BRAINSTEM 'GAZE CENTRES'
- Midbrain reticular formation

⇒ Pineal gland

⇒ Third ventricle

↓

- Interstitial nucleus of Cajal

↓

∅ Posterior commissure

↓

- Oculomotor nuclei (CNIII)
- Trochlear nuclei (CNIV)

CONDITION/S ASSOCIATED WITH[13,134,138, 141]

Common

- Pinealoma
- Hydrocephalus
- Progressive supranuclear palsy (PSP)

Less common

- Multiple sclerosis
- Wernicke's encephalopathy
- Tay–Sachs disease
- AIDS encephalopathy
- Whipple's disease

MECHANISM/S

The midbrain reticular formation (MRF) mediates vertical gaze and vergence eye movements.[138]

Upward gaze paresis is caused by:

1. posterior commissure lesion.

Downward gaze paresis and combined upgaze and downgaze paresis are caused by:

1. bilateral rostral interstitial medial longitudinal fasciculus (riMLF) lesions.

Posterior commissure lesion

A lesion in the posterior commissure will result in vertical gaze palsy due to a loss of input from the interstitial nucleus of Cajal to the oculomotor nuclei, resulting in weakness of the superior rectus muscle and inferior oblique muscle.

Bilateral riMLF lesions

Bilateral riMLF lesions result in loss of neural input to the oculomotor nuclei and trochlear nuclei, resulting in weakness of the inferior rectus muscle and superior oblique muscles, respectively.[1] In combined upgaze and downgaze palsy there is weakness of the superior rectus muscle, inferior rectus muscle, inferior oblique muscle and superior oblique muscle.

SIGN VALUE

Vertical gaze palsy is a sign of a midbrain lesion.

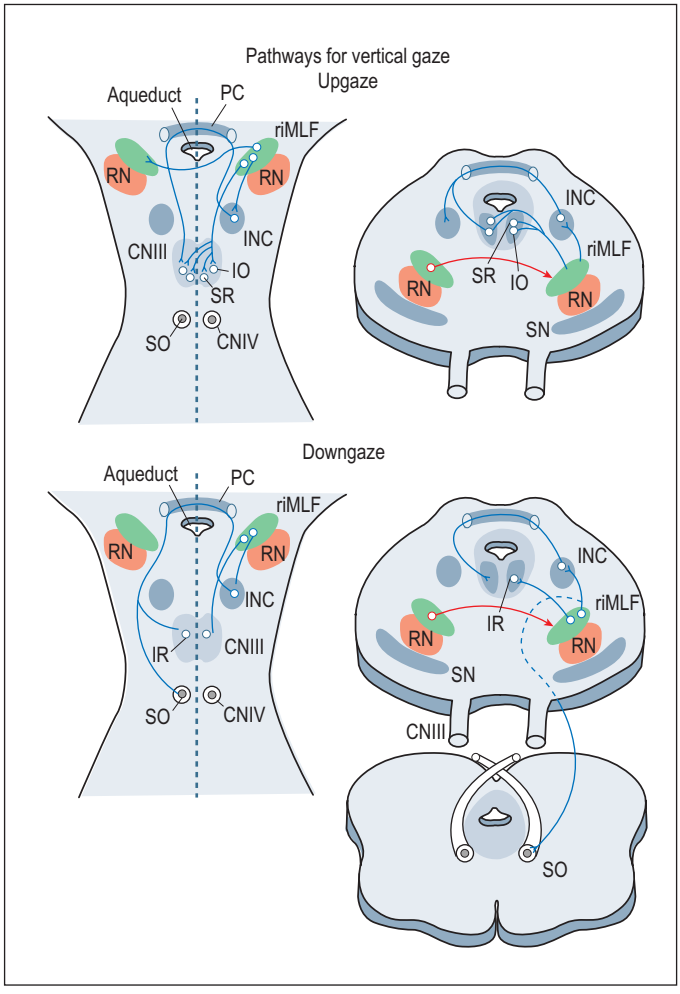


Figure 5.103 Neural pathways associated with vertical gaze

Upgaze pathways originate in the rostral interstitial nucleus of the medial longitudinal fasciculus (MLF) and project dorsally to innervate the oculomotor and trochlear nerves, traveling through the posterior commissure. Upgaze paralysis is a feature of the dorsal midbrain syndrome as a result of the lesion's effect on the posterior commissure. Downgaze pathways also originate in the rostral interstitial nucleus of the MLF but probably travel more ventrally. Bilateral lesions are also needed to affect downgaze and usually are located dorsomedial to the red nucleus. INC = interstitial nucleus of Cajal; IO = inferior oblique subnucleus; IR = inferior rectus subnucleus; PC = posterior commissure; riMLF = rostral interstitial nucleus of the medial longitudinal fasciculus; RN = red nucleus; SN = substantia nigra; SO = superior oblique subnucleus; SR = superior rectus subnucleus.

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn. St Louis: Mosby, 2008: Fig 9-13-4.

Visual acuity

DESCRIPTION

Visual acuity is a *vital sign* of the eye. Visual acuity is assessed using the Snellen chart. Decreased visual acuity is characterised by a patient who is unable to read the 6/9 line or has a significant change in visual acuity from baseline. Patients with refractive errors use their glasses or use a pinhole refractor during the examination to compensate for refractive error.[208]

(*Note*: this section will focus on neurological conditions associated with visual acuity abnormalities. An ophthalmology text should be consulted for further information.)

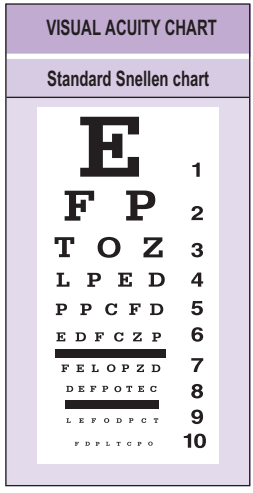


Figure 5.104 Snellen chart

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 2-6-7.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

Nervous system

PRECHIASMAL STRUCTURES
- Retinal epithelium

↓
- Optic nerve

⇒ Orbital apex

⇒ Optic canal, sphenoid bone

↓

CHIASMAL STRUCTURES
- Optic chiasm

⇒ Pituitary gland

⇒ Cavernous sinus

↓

POSTCHIASMAL STRUCTURES
- Optic tracts

↓
- Lateral geniculate nucleus (LGN), thalamus

↓
- Superior optic radiation, parietal lobe ('Baum's loop')

↓
- Inferior optic radiation, temporal lobe ('Meyer's loop')

↓
- Optic cortex, occipital lobe

EYE
- Cornea
- Anterior chamber
- Lens
- Posterior chamber
- Vitreous body
- Retinal epithelium

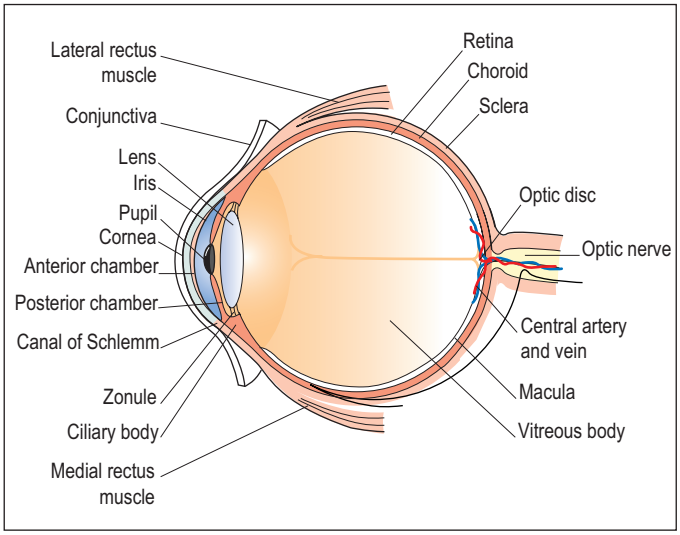


Figure 5.105 Anatomy of the eye

Reproduced, with permission, from Goldman L, Ausiello D, *Cecil Medicine*, 23rd edn, Philadelphia: Saunders, 2007: Fig 449-2.

CONDITION/S ASSOCIATED WITH[6,209]

COMMON

- Bilateral occipital lobe infarction
- Bilateral occipital lobe haemorrhage
- Optic neuritis
- Elevated intracranial pressure (e.g. idiopathic intracranial hypertension, mass lesion)

LESS COMMON

- Ocular migraine
- Anterior ischaemic optic neuropathy (AION)
- Orbital apex syndrome
- Mass lesion (e.g. tumour, abscess, AVM)
- Cerebral venous sinus thrombosis

MECHANISM/S

Neurological conditions associated with decreased visual acuity include:

1. unilateral or bilateral prechiasmal lesions
2. bilateral postchiasmal lesions.

Chiasmal lesions and unilateral postchiasmal lesions are not usually associated with decreased visual acuity. Rather, they typically cause visual field defects. See 'Visual field defects' in this chapter.

Unilateral or bilateral prechiasmal lesion(s)

Unilateral prechiasmal lesions (e.g. optic glioma, optic neuritis) result in ipsilateral monocular visual loss. Associated features may include papilloedema, optic atrophy and a relative afferent pupillary defect (RAPD). The intracranial segments of the optic nerves are supplied by branches of the anterior cerebral, middle cerebral and anterior communicating arteries. Due to the extensive blood supply of these structures, infarction is rare.[210]

Bilateral postchiasmal lesions

Bilateral occipital lobe lesions (e.g. infarction, haemorrhage) result in a cortical blindness. Patients may be unaware of the abnormality (i.e., anosognosia).

SIGN VALUE

In a study of 317 new patients, near visual acuity of 6/12 (i.e., 20/40) or worse had a sensitivity of 75%, specificity of 74% and LR of 2.8 for detection of significant ocular disease.[211] Distance visual acuity testing of 6/9 (i.e., 20/30) or worse had a sensitivity of 74%, specificity of 73% and LR of 2.7 for detection of significant ocular disease.[211]

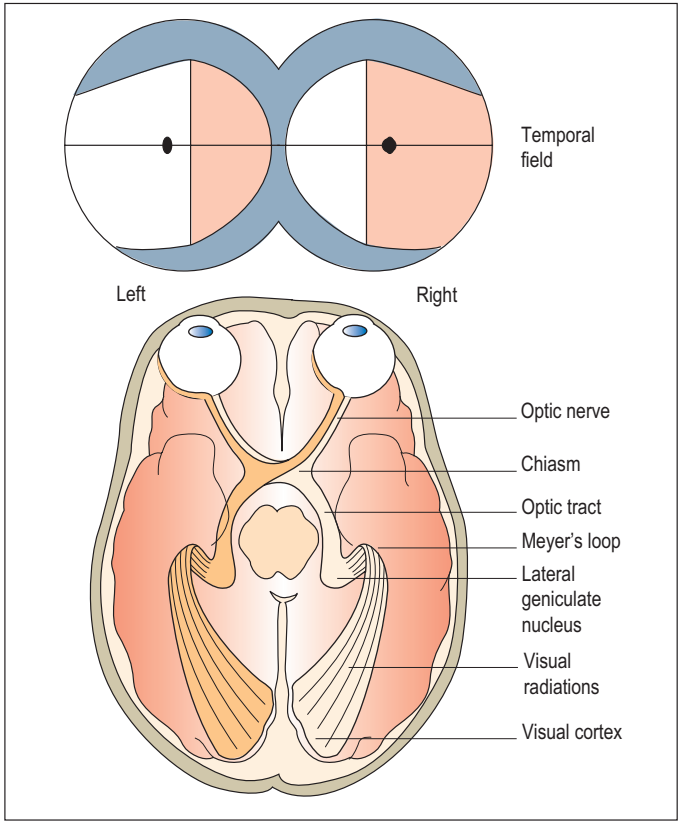


Figure 5.106 The visual pathways

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 39-1.

Visual field defects

DESCRIPTION

Visual field defects are partial deficits in the normal field of vision. The extent of the normal visual field (in the primary gaze position) is approximately 90° temporally, 50° superiorly, 50° nasally and 60° inferiorly.[140]

Visual field defects are detected at the bedside using the confrontation technique. Simultaneous testing of two quadrants is clinically useful in suspected parietal lobe lesions to detect visual hemineglect. In visual hemineglect, the patient may perceive the moving object in the left visual hemifield in isolation, but may be unable to perceive the object when simultaneous visual stimuli are presented to both visual fields.[4,212]

CONDITION/S ASSOCIATED WITH

Common

- PCA territory infarction
- MCA territory infarction
- Occipital lobe haemorrhage
- Age-related macular degeneration

Less common

- Retinitis pigmentosa
- Pituitary macroadenoma
- Craniopharyngioma
- Central retinal artery branch occlusion
- Multiple sclerosis

MECHANISM/S

The causes of visual field defects (see Table 5.33) are divided into the following categories:

1. disorders of the prechiasmal structures
2. disorders of the optic chiasm
3. disorders of the postchiasmal structures.

In general, visual field defects that cross the vertical meridian (vertical line dividing each visual hemifield) are due to prechiasmal lesions or primary eye disorders.[4] Visual field defects that do not cross the vertical meridian, such as in homonymous hemianopia, are caused by chiasmal or postchiasmal lesions.[4]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

Eye

- Cornea
- Anterior chamber
- Lens
- Posterior chamber
- Vitreous body
- Retinal epithelium

Neurological structures

PRECHIASMAL STRUCTURES

- Retinal epithelium

↓

- Optic nerve

⇒ Orbital apex

⇒ Cavernous sinus

⇒ Optic canal, sphenoid bone

↓

CHIASMAL STRUCTURES

- Optic chiasm

⇒ Pituitary gland

↓

POSTCHIASMAL STRUCTURES

- Optic tracts

↓

- Lateral geniculate nucleus (LGN), thalamus

↓

- Superior optic radiation ('Baum's loop'), parietal lobe

↓

- Inferior optic radiation ('Meyer's loop'), temporal lobe

↓

- Optic cortex, occipital lobe

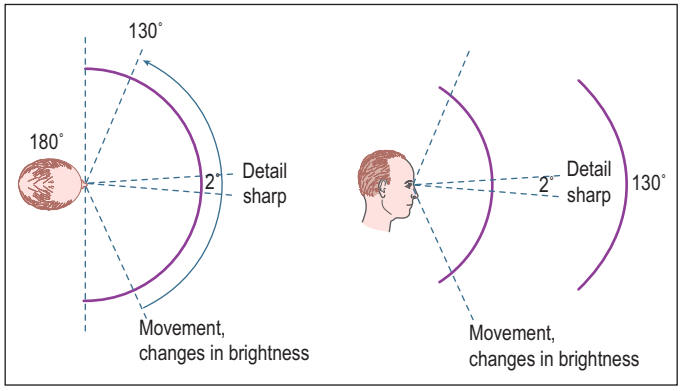


Figure 5.107 Extent of the normal visual field

Based on the Scottish Sensory Centre, Functional assessment of vision. Available: http://www.ssc.education.ed.ac.uk/courses/vi&multi/vmay06c.html [5 Apr 2011].

TABLE 5.33 Mechanisms of visual fields defects[4,8,211,213]

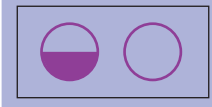
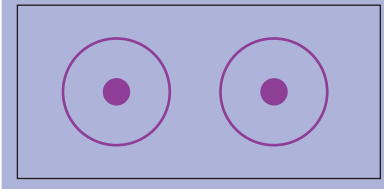
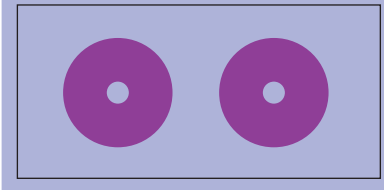
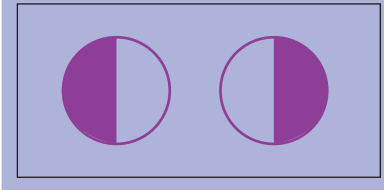
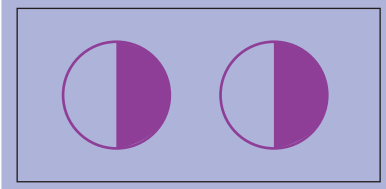
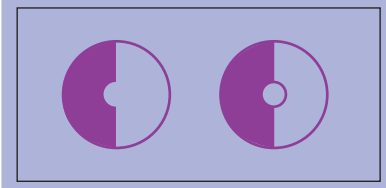
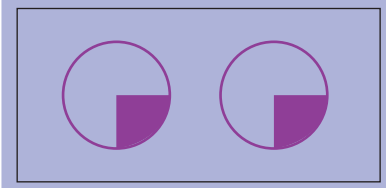
Visual field defect	Mechanism(s)
Altitudinal scotoma  **FIGURE 5.108**	• Branch central retinal artery occlusion • Retinal detachment • Partial optic nerve lesion
Central scotoma  **FIGURE 5.109**	• Macular degeneration • Optic nerve lesion
Constricted visual field ('tunnel vision')  **FIGURE 5.110**	• Glaucoma • Retinitis pigmentosa • Central retinal artery occlusion with ciliretinal artery sparing • Chronic papilloedema
Bitemporal hemianopia  **FIGURE 5.111**	• Optic chiasm lesion

TABLE 5.33 Mechanisms of visual fields defects—cont'd

Visual field defect	Mechanism(s)
Homonymous hemianopia  **FIGURE 5.112**	• Optic cortex lesion • Superior and inferior optic radiations lesion • LGN, thalamus lesion • Optic tract lesion (least common)
Homonymous hemianopia with macular sparing  **FIGURE 5.113**	• Occipital pole lesion
Homonymous quadrantanopia  **FIGURE 5.114**	• Optic radiation lesion

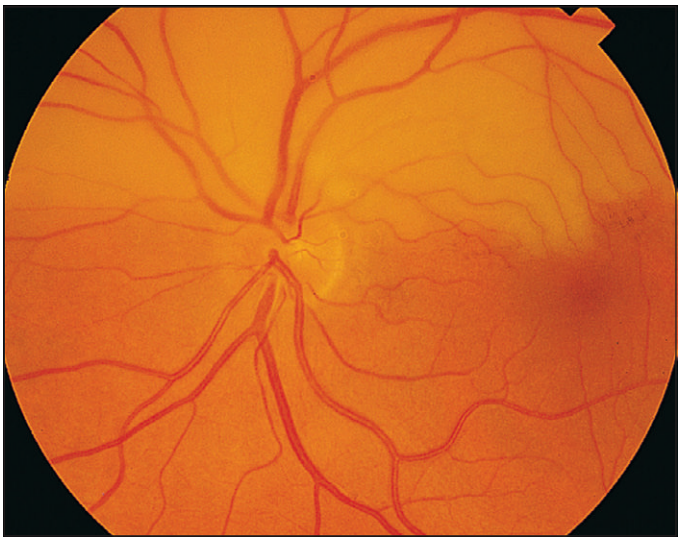


Figure 5.115 Superior retinal infarction (pale region) due to branch retinal artery occlusion, resulting in inferior altitudinal scotoma

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 6-16-6.

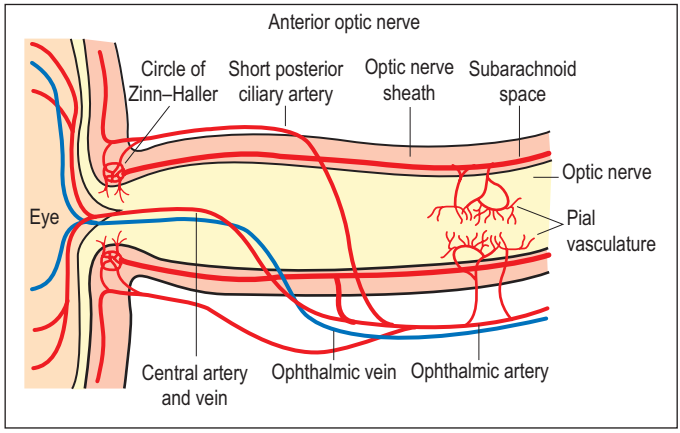


Figure 5.116 Anatomy of the vascular supply of the anterior optic nerve

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn. St Louis: Mosby, 2008: Fig 9-2-3.

Prechiasmal disorders

Unilateral prechiasmal disorders cause ipsilateral monocular visual field defects that may cross the vertical meridian (i.e., the vertical line 'bisecting' the visual field).[4]

ALTITUDINAL SCOTOMA – BRANCH CENTRAL RETINAL ARTERY OCCLUSION

Occlusion of the superior or inferior branch central retinal artery may cause infarction of the superior or inferior half of the retina, resulting in an inferior or superior altitudinal scotoma, respectively.

CONSTRICTED VISUAL FIELD – CENTRAL RETINAL ARTERY OCCLUSION [CRAO] WITH CILIORETINAL ARTERY SPARING

The cilioretinal artery supplies the macula and fovea (e.g., the central portions of the visual space). CRAO with cilioretinal artery sparing thus causes infarction of the retinal neuroepithelium, with the exception of the most central region, resulting in a constricted visual field defect.[212]

CONSTRICTED VISUAL FIELD – RETINITIS PIGMENTOSA

The most common form of retinitis pigmentosa causes progressive loss of peripheral retinal rod photoreceptors, resulting in impaired vision in low light and loss of the peripheral vision (i.e., a constricted visual field).[213]

CENTRAL SCOTOMA – DISORDERS OF THE OPTIC NERVE

The area where the optic nerve enters the retina corresponds to the location of the physiological blindspot that is due to the absence of retinal photoreceptors in this region. Optic nerve disorders may cause enlargement of the physiological blind spot and/or central scotoma.[3]

CENTRAL SCOTOMA – MACULAR DEGENERATION

Disorders of the macula are due to injury to the retina in the foveal and parafoveal regions, resulting in a central scotoma.[212] The fovea represents the region with the largest density of rods and highest visual acuity at the site of fixation (i.e., the most central portion of the visual field).

Optic chiasm lesions

Optic chiasm lesions cause dysfunction of the nerve fibres supplying the medial hemiretinas, and thus result in bitemporal hemianopia. Optic chiasm lesions typically result from compression by an adjacent mass. The most common cause is a pituitary macroadenoma. Other causes include craniopharyngioma and pituitary apoplexy.[211] Associated features of optic chiasm lesions include disruption of the hypothalamic–pituitary axis, headache and hydrocephalus.[210]

Postchiasmal disorders

Postchiasmal disorders cause homonymous visual field defects. Nerve fibres from the optic cortex, optic radiations and lateral geniculate nucleus (LGN) of the thalamus contain fibres that supply the ipsilateral temporal hemiretina and the contralateral medial hemiretina.[4,6] Fibres destined for the contralateral hemiretina cross at the optic chiasm.

HOMONYMOUS HEMIANOPIA WITH MACULAR SPARING

Occipital lobe lesions sparing the posterolateral striate cortex, which contains the fibres representing the macula and fovea, may result in homonymous hemianopia with macular sparing.[212] The fovea and macula together make up a small percentage of the total area of the retina but are supplied by a relatively large number of nerve fibres. Due to the relatively large representation, incomplete occipital lobe lesions may spare enough of these fibres to preserve central vision.[210,211]

SIGN VALUE

In detecting a visual field defect of prechiasmal origin, the confrontation technique has a sensitivity of 11–58%, specificity of 93–99% and LR of 6.1.[214–218]

In detecting a visual field defect of chiasmal or postchiasmal origin, the confrontation technique has a sensitivity of 43–86%, specificity of 86–95% and LR of 6.8.[214–218]

Refer to Table 5.34 for clinical utility of hemianopia in unilateral cerebral hemisphere lesions.

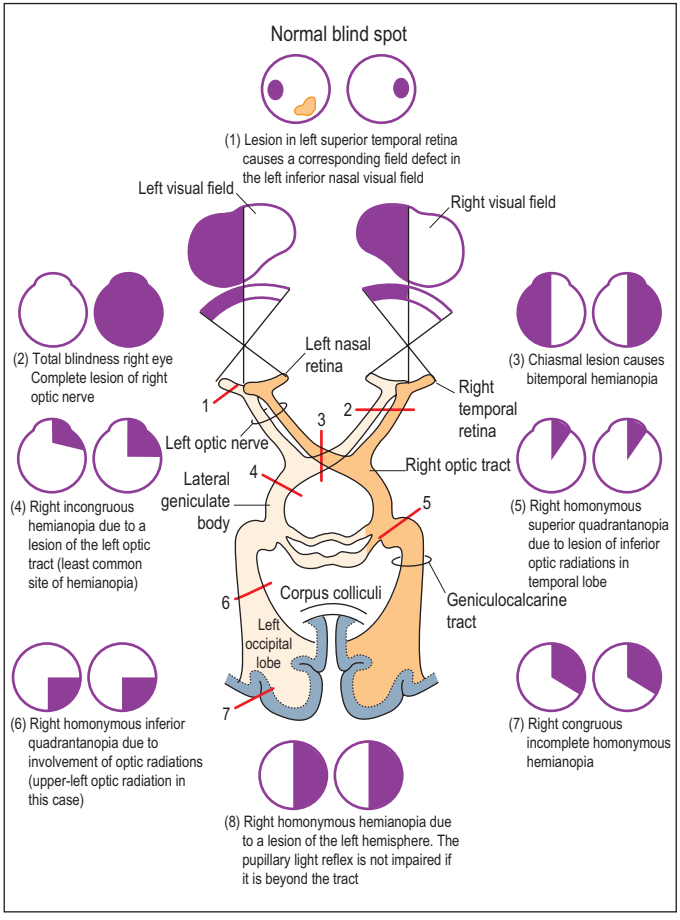


Figure 5.117 Topographical mechanisms of visual field defects

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 14-3.

TABLE 5.34 Clinical utility of hemianopia in unilateral cerebral hemisphere lesions[40]

	Sensitivity	Specificity	Positive LR	Negative LR
Hemianopia[40]	30%	98%	NS	0.7

Adapted from McGee S, *Evidence Based Physical Diagnosis*, 2nd edn, St. Louis: Saunders, 2007.

Waddling gait (bilateral Trendelenburg gait)

DESCRIPTION

Exaggerated rotation of the pelvis and pronounced lower limb swing compensate for bilateral proximal leg and hip girdle muscle weakness.[28,43] Pelvic instability results in a characteristic stance of slight hip flexion and exaggerated lumbar lordosis.[28] Weakness of the hip extension also impairs the patient's ability to stand from a squatting position.[28] Patients may use their hands to push themselves up to stand from a squatting position (i.e., Gowers' sign).[28]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

× Proximal muscle groups

CONDITION/S ASSOCIATED WITH[219]

Common

- Muscular dystrophy (e.g. limb girdle muscular dystrophy, Duchenne's muscular dystrophy)
- Metabolic myopathy (e.g. thyroid myopathy)

Less common

- Polymyositis
- Dermatomyositis
- Mitochondrial myopathy
- Glucocorticoid-induced myopathy

MECHANISM/S

A waddling gait is caused by proximal muscle weakness. Proximal muscle weakness is most commonly associated with primary muscle disorders (myopathy).[52] Proximal muscle weakness and pelvic girdle instability result in a characteristic stance of slight hip flexion and exaggerated lumbar lordosis to maintain balance during gait examination.

SIGN VALUE

Waddling gait is a sign of proximal muscle weakness.

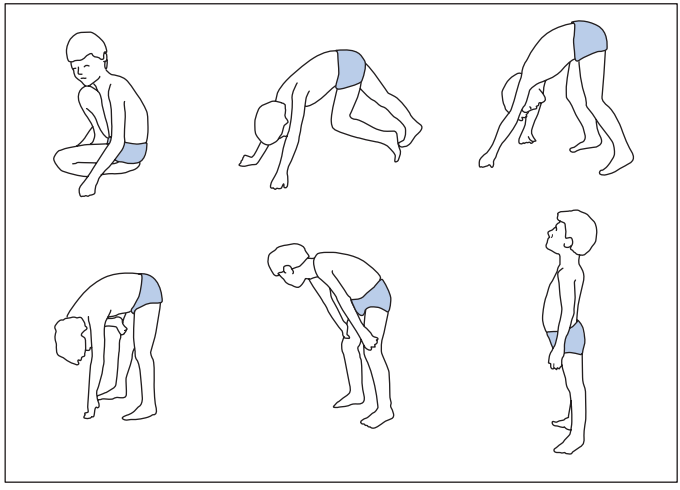


Figure 5.118 Gowers' sign in proximal muscle weakness

Reproduced, with permission, from Canale ST, Beaty JH, *Campbell's Operative Orthopaedics*, 11th edn, St Louis: Mosby, 2007: Fig 32-5.

Wallenberg's syndrome (lateral medullary syndrome)

DESCRIPTION

Lateral medullary syndrome is a brainstem vascular syndrome characterised by:

- uvular deviation away from the side of the lesion
- ipsilateral impaired palatal elevation
- dysarthria, dysphagia, hoarseness
- ipsilateral facial sensory loss
- ipsilateral Horner's syndrome
- ipsilateral cerebellar ataxia
- contralateral loss (pain and temperature) below the lesion.

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

BRAINSTEM

- Nucleus ambiguus (CNIX/X)
- Trigeminal sensory nuclei (CNV)
- Descending sympathetic fibres
- Spinocerebellar tract
- Spinothalamic tracts

CONDITION/S ASSOCIATED WITH[121]

Common

- Posterior inferior cerebellar artery (PICA) territory infarction
- Vertebral artery insufficiency

MECHANISM/S

Posterior inferior cerebellar artery (PICA) territory infarction may result in dysfunction of multiple brainstem nuclei in the lateral medulla. See Table 5.35 for mechanisms of the clinical findings in lateral medullary syndrome.

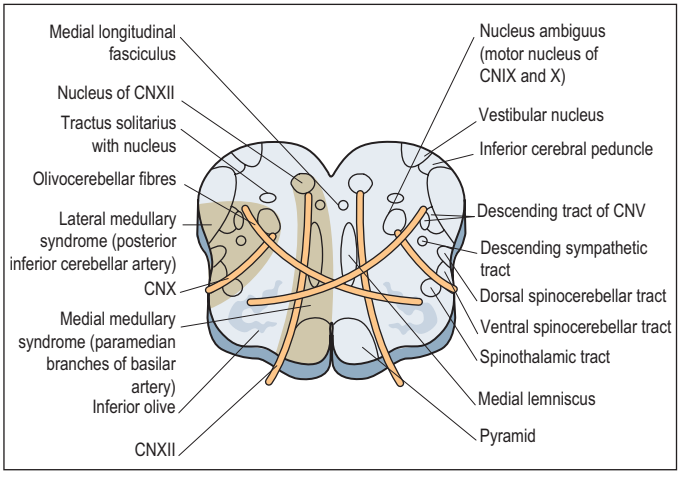


Figure 5.119 Affected brainstem nuclei and long tracts in lateral medullary syndrome (lateral shaded area)

Reproduced, with permission, from Flint PW et al, *Cummings Otolaryngology: Head and Neck Surgery*, 5th edn, Philadelphia: Mosby, 2010: Fig 166-4.

TABLE 5.35 Mechanisms of features of lateral medullary syndrome

Clinical signs	Nerve dysfunction
• Uvular deviation away from side of lesion • Ipsilateral palatal elevation • Dysarthria • Dysphagia • Hoarseness	→ Nucleus ambiguus (CNIX, X)
• Ipsilateral facial sensory loss	→ Descending tract, CNV
• Ipsilateral Horner's syndrome	→ Descending sympathetic fibres
• Ipsilateral cerebellar ataxia	→ Spinocerebellar tracts
• Contralateral loss (pain and temperature) below lesion	→ Spinothalamic tract

Weakness

DESCRIPTION

Muscle weakness is characterised by the grade of weakness, anatomical distribution and associated findings (e.g. lower motor neuron signs, upper motor neuron signs, cortical localising signs).

Muscle weakness is graded according to the system developed by the British Medical Research Council (MRC) during World War II (see Table 5.36).[220]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

UPPER MOTOR NEURON
- Motor cortex

↓
- Corona radiata, subcortical white matter

↓
- Posterior limb, internal capsule

↓
- Pyramidal tracts, medial brainstem

↓

∅ Pyramidal decussation, medulla

↓
- Lateral corticospinal tracts, spinal cord

⇒ Central canal, spinal cord

↓

LOWER MOTOR NEURON
- Anterior horn grey matter, spinal cord

↓
- Nerve root

⇒ Intervertebral disc

⇒ Intervertebral foramen

↓
- Nerve plexus (e.g. brachial plexus)

↓
- Peripheral nerve

⇒ Potential sites of nerve entrapment (e.g. carpal tunnel)

↓

NEUROMUSCULAR JUNCTION
- Neuromuscular junction

↓

MUSCLE

× Muscle

TABLE 5.36 British Medical Research Council System of Grading Muscle Power[220]

Grade	Feature(s)
0/5	No contraction
1/5	Muscle flicker
2/5	Any movement, but not against gravity
3/5	Movement against gravity, no movement against resistance
4–/5	Movement against gravity but barely against resistance
4/5	Movement against gravity and resistance
4+/5	Movement against gravity and almost full power against resistance
5/5	Normal power

Adapted from McGee S, *Evidence Based Physical Diagnosis*, 2nd edn, St. Louis: Saunders, 2007.

CONDITION/S ASSOCIATED WITH

Common
- MCA territory infarction
- Cerebral haemorrhage
- Lacunar infarction, posterior limb internal capsule
- Myelopathy
- Compression mononeuropathy (e.g. carpal tunnel syndrome)
- Radiculopathy
- Hypokalaemia

Less common
- Multiple sclerosis
- Peripheral neuropathy
- ACA territory infarction
- Guillain–Barré syndrome
- Myasthenia gravis
- Myopathy
- Todd's paralysis
- Hypoglycaemia
- Poliomyelitis

MECHANISM/S

Mechanisms of weakness are grouped according to the anatomical distribution and associated findings (e.g. upper motor

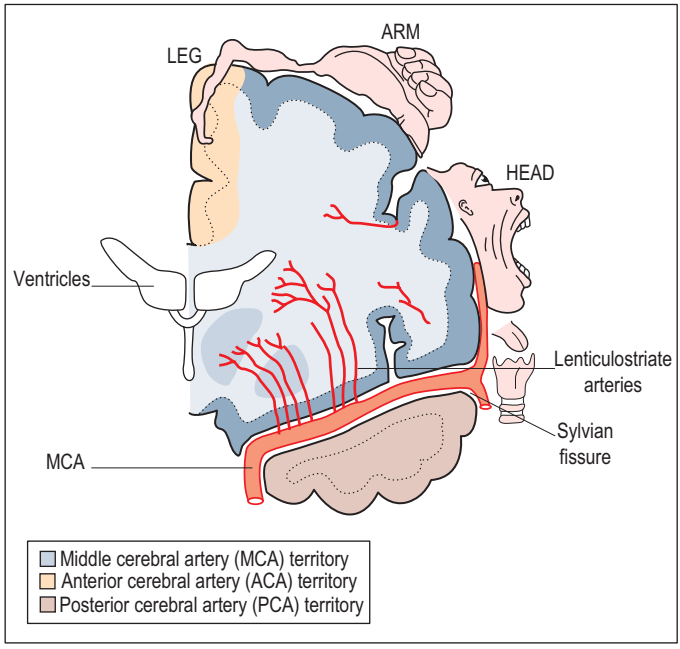


Figure 5.120 Anterior circulation and somatotopic organisation, motor cortex

Reproduced, with permission, from Lewandowski CA, Rao CPV, Silver B, Ann Emerg Med 2008; 52(2): S7–S16, Fig 7.

neuron findings, lower motor neuron findings, cortical localising signs etc). See Tables 5.37 and 5.38.

The mechanisms of weakness include:

1. motor cortex lesion
2. posterior limb, internal capsule lesion
3. medial brainstem lesion
4. spinal cord lesion
5. radiculopathy
6. Guillain–Barré syndrome
7. peripheral neuropathy
8. disorders of the neuromuscular junction
9. myopathy
10. metabolic, toxicological and infectious disorders.

Motor cortex lesion

Results in contralateral hemiparesis in the somatotopic distribution of the motor cortex (i.e., the homunculus). Associated upper motor neuron signs are characteristic. Immediately following acute ischaemic infarction of the motor cortex hypotonia, flaccid paresis and hyporeflexia or areflexia may be present. Spasticity and hyperreflexia develop days to weeks later.[55]

Posterior limb, internal capsule lesion

Causes contralateral pure motor hemiparesis of the face, arm and leg. Associated upper motor neuron signs are characteristic. Due to the close proximity of motor fibres to one another in the posterior limb of the internal capsule, even small lesions may result in pure hemimotor findings in the face, arm and leg. The most common cause is lacunar infarction.

Medial brainstem lesion

Medial brainstem lesions may affect cranial nerve motor nuclei and/or the descending long tracts of motor fibres.[221] Brainstem lesions are characterised by motor and/or sensory findings that cross the midline (e.g. ipsilateral cranial nerve findings and contralateral long tract findings). Causes include medial brainstem vascular syndromes, haemorrhagic infarction, multiple sclerosis and tumours.

Spinal cord lesion

Unilateral spinal cord lesions affecting the lateral cortical spinal tract cause ipsilateral weakness. The upper motor neuron fibres have crossed in the pyramidal decussation in the medulla. Associated upper motor neuron signs are characteristic.

Radiculopathy

Motor findings occur in the distribution of a nerve root(s). Lesions of the nerve root typically cause positive (e.g. pain) and negative (e.g. decreased sensation) sensory

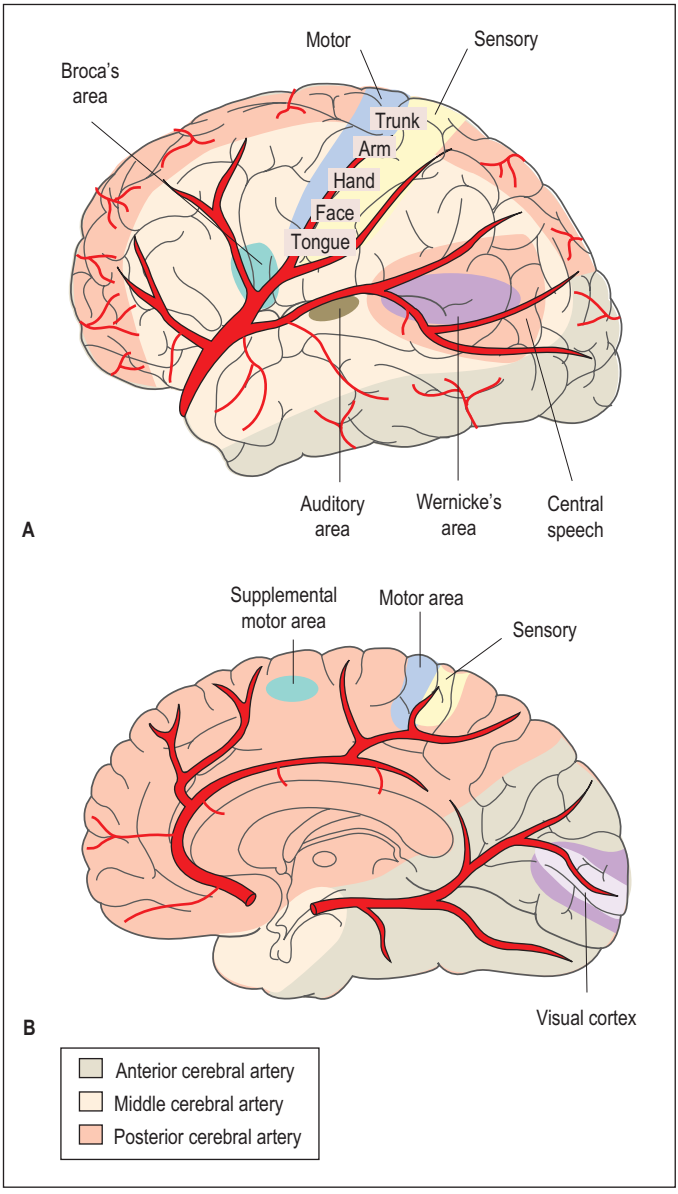


Figure 5.121 Vascular territories of the cerebral arteries

A, Lateral aspect of the cerebral cortex; **B**, medial aspect of the cerebral cortex.

Reproduced, with permission, from Goldman L, Ausiello D, *Cecil Medicine*, 23rd edn, Philadelphia: Saunders, 2007: Fig 430-3.

abnormalities in the distribution of one or more nerve roots. Lower motor neuron signs are characteristic. Mechanical injury to the nerve root causes degeneration of the axons and myelin distal to the site of injury (i.e., Wallerian degeneration), resulting in sensory and motor deficits in the distribution of the affected nerve root. Common causes include spondylosis, intervertebral disc disease and tumours. See Table 5.38.

Guillain–Barré syndrome (GBS)

Guillain–Barré syndrome (GBS), or acute inflammatory demyelinating polyradiculopathy, is characterised by demyelination with variable axonal

Text continued on page 433.

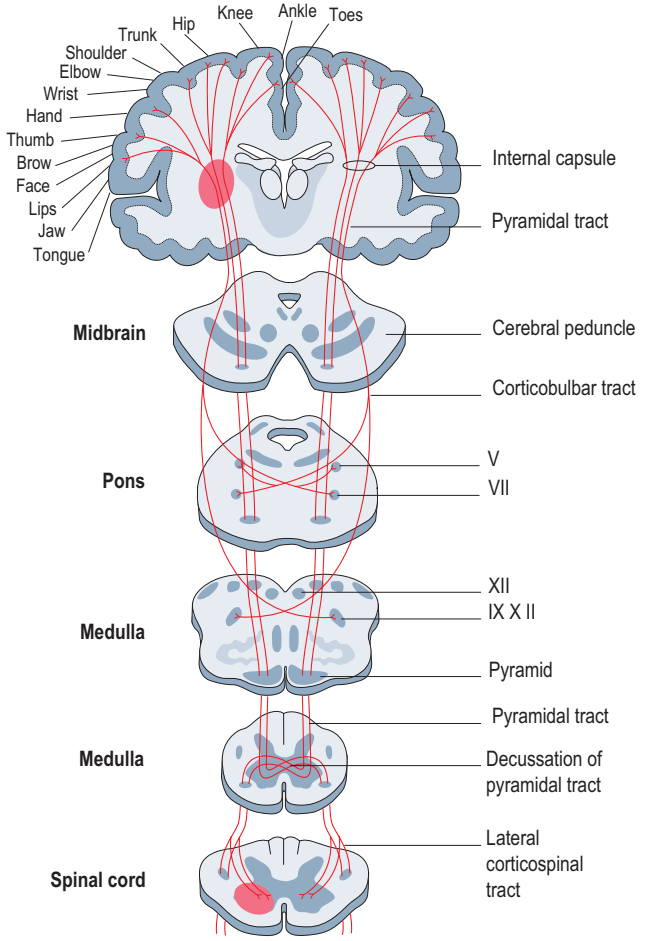


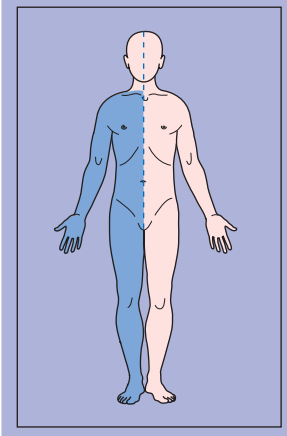
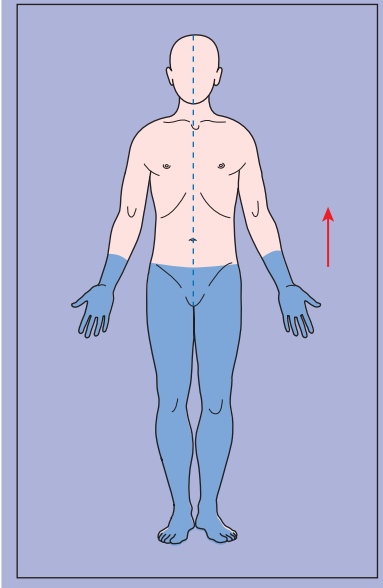
Figure 5.122 Upper motor neuron anatomy

Reproduced, with permission, from Clark RG, *Manter and Gatz's Essential Neuroanatomy and Neurophysiology*, 5th edn, Philadelphia: FA Davis Co, 1975.

TABLE 5.37 Upper and lower motor neuron signs

Upper motor neuron signs	Lower motor neuron signs
• Spasticity	• Fasciculations
• Clonus	• Muscle atrophy
• Weakness	• Hypotonia
• Hyperreflexia	• Weakness
• Babinski sign	• Hyporeflexia/areflexia

TABLE 5.38 Mechanisms of weakness based on the pattern of clinical findings

Pattern of weakness	Mechanism(s)
Arm and leg  **FIGURE 5.123**	• Contralateral motor cortex lesion • Ipsilateral cervical spinal cord lesion • Contralateral posterior limb, internal capsule lesion • Todd's paralysis
Ascending weakness  **FIGURE 5.124**	• Guillain–Barré syndrome • Tick paralysis

Continued

TABLE 5.38 Mechanisms of weakness based on the pattern of clinical findings—cont'd

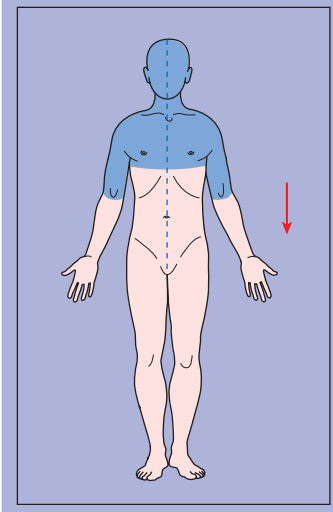
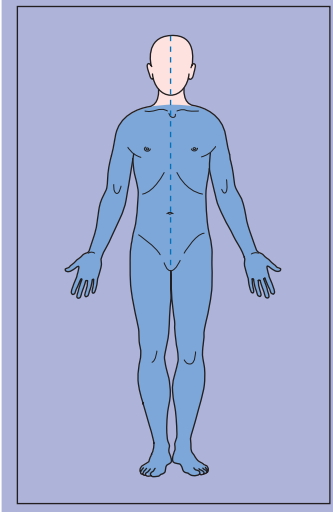
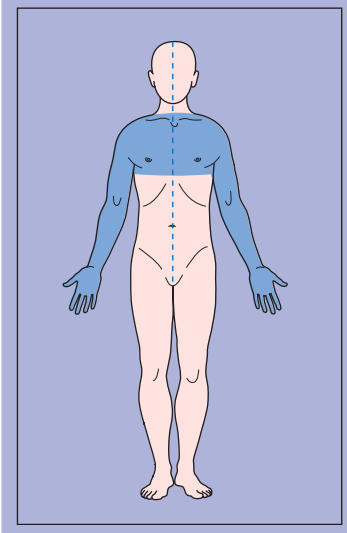
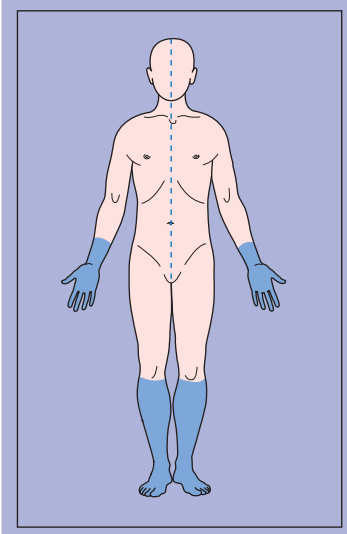
Pattern of weakness	Mechanism(s)
Descending weakness  FIGURE 5.125	• Botulism • Miller Fisher variant Guillain–Barré syndrome • Diphtheria polyneuropathy
Bilateral arms and legs  FIGURE 5.126	• Complete cervical spinal cord lesion • Anterior cord syndrome

TABLE 5.38 Mechanisms of weakness based on the pattern of clinical findings—cont'd

Pattern of weakness	Mechanism(s)
Bilateral upper limbs  **FIGURE 5.127**	• Cervical syringomyelia • Cervical radiculopathy
Distal muscle groups  **FIGURE 5.128**	• Peripheral neuropathy • Myotonic dystrophy

Continued

TABLE 5.38 Mechanisms of weakness based on the pattern of clinical findings—cont'd

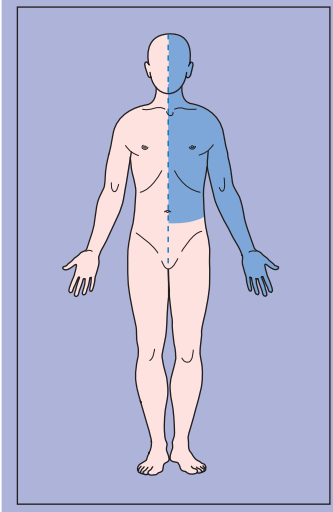
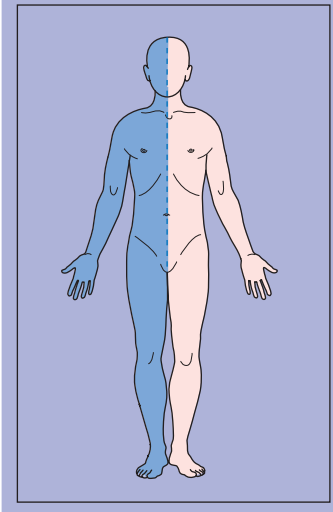
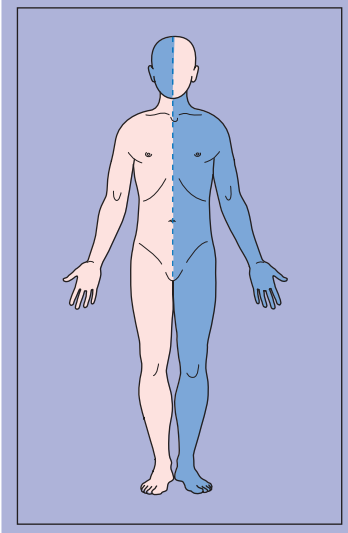
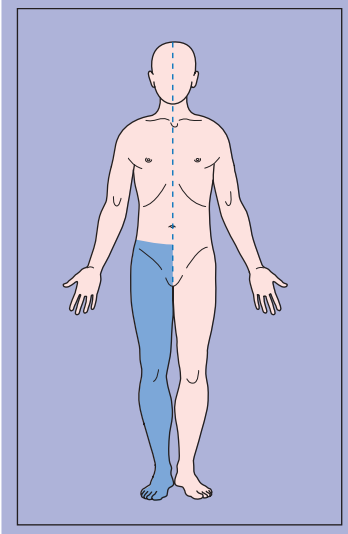
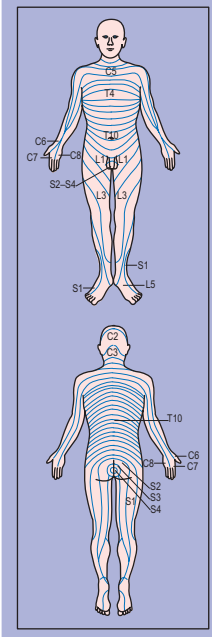
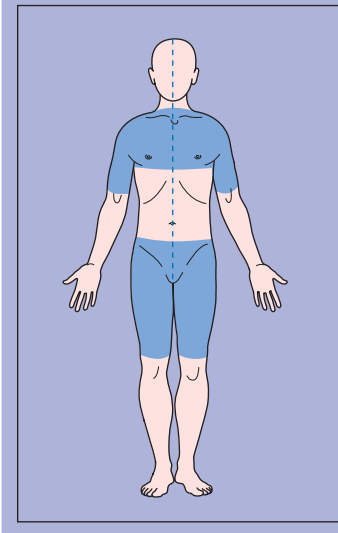
Pattern of weakness	Mechanism(s)
Face and arm  FIGURE 5.129	• MCA territory infarction
Face, arm and leg  FIGURE 5.130	• Posterior limb, internal capsule lesion • ICA territory (ACA + MCA) infarction

TABLE 5.38 Mechanisms of weakness based on the pattern of clinical findings—cont'd

Pattern of weakness	Mechanism(s)
Face and contralateral arm and leg  **FIGURE 5.131**	• Brainstem lesion
Leg  **FIGURE 5.132**	• Lumbar radiculopathy • ACA territory infarction • Unilateral spinal cord lesion below T1

Continued

TABLE 5.38 Mechanisms of weakness based on the pattern of clinical findings—cont'd

Pattern of weakness	Mechanism(s)
Peripheral nerve distribution	• Compression mononeuropathy
Nerve root distribution  **FIGURE 5.133**	• Radiculopathy
Proximal muscle groups  **FIGURE 5.134**	• Myopathy
Distal muscle groups	• Length-dependent peripheral neuropathy

degeneration and lymphocytic infiltration and is associated with several preceding infectious illnesses (e.g. *Campylobacter jejuni*, herpes viruses, *Mycoplasma pneumoniae*).[222] GBS typically causes flaccid paresis in the distal musculature, which progresses proximally (i.e., an ascending pattern of weakness). Lower motor neuron signs are characteristic.

Peripheral neuropathy

Causes include compression mononeuropathy and length-dependent peripheral neuropathy.

COMPRESSION MONONEUROPATHY

Mechanical injury causes degeneration of the axons and myelin distal to the site of injury (i.e., Wallerian degeneration), resulting in motor and sensory deficits in the distribution of the affected peripheral nerve.[220] Causes include carpal tunnel syndrome, common peroneal nerve palsy and radial nerve palsy (e.g. 'Saturday night' palsy).

LENGTH-DEPENDENT PERIPHERAL NEUROPATHY

Length-dependent peripheral neuropathy may result from failure of the perikaryon to synthesise enzymes or proteins, dysfunction in axonal transport or disturbances in energy metabolism.[220] A variety of metabolic abnormalities within the peripheral nerve result in degeneration of the distal nerve fibres, which progresses proximally.[220] Causes include diabetes mellitus, alcohol and inherited neuropathies.[220]

Disorders of the neuromuscular junction

Myasthenia gravis is caused by antibodies directed against acetylcholine receptors on the postsynaptic neuromuscular membrane. Myasthenia gravis typically involves muscles of the eyes and face, and muscle strength that decreases with activity (i.e., fatiguability). Lambert–Eaton syndrome is a paraneoplastic syndrome associated with small-cell lung carcinoma, and is caused by antibodies against presynaptic calcium channels.[223] Characteristics include proximal muscle weakness and weakness that transiently improves with increased activity.[223]

Myopathy

Myopathies typically cause proximal weakness. One exception is myotonic dystrophy, which preferentially affects cranial and distal muscle groups. Causes of myopathy include muscular dystrophy, metabolic myopathy and inflammatory myopathy.

Metabolic, toxicological and infectious disorders

Metabolic and toxic disorders may cause muscle weakness due to changes in the excitability (i.e., resting membrane potential) of nerve fibres and/or muscle fibres, or due to direct toxic effects to nerves or muscles. Causes include hypokalaemia, hypocalcaemia, hypoglycaemia, strychnine toxicity, tetanus, and botulism.

CLOSTRIDIUM BOTULINUM

Botulism is caused by the bacterium *Clostridium botulinum*, which produces a toxin that blocks the release of acetylcholine at the motor terminal.[133]

TICK PARALYSIS

Tick paralysis is caused by a toxin produced by the tick during feeding, which augments axonal sodium flux across the membrane without affecting the neuromuscular junction.[224,225] Motor nerve terminal function rapidly improves after tick removal.[224] Characteristics include ascending flaccid paresis and acute ataxia, which may progress to bulbar involvement and respiratory arrest.[225]

SIGN VALUE

The grade, distribution and progression of weakness, and associated findings (e.g. lower motor neuron signs, upper motor neuron signs, cortical localising signs) are important when considering potential aetiologies of weakness.

Wernicke's aphasia (receptive aphasia)

DESCRIPTION

Receptive aphasia is a disorder of language comprehension. Speech fluency (i.e., word production) is typically not affected. The patient's speech is meaningless or strange and may contain paraphasic errors (i.e., inappropriate word substitutions based on meaning or sound).[6,46]

RELEVANT NEUROANATOMY AND TOPOGRAPHICAL ANATOMY

- Wernicke's area – posterior superior temporal gyrus, dominant hemisphere

⇒ Inferior division, middle cerebral artery (MCA)

CONDITION/S ASSOCIATED WITH[6,66]

Common

- MCA territory infarction
- Cerebral haemorrhage
- Vascular dementia
- Migraine (transient)

Less common

- Alzheimer's disease
- Mass lesion (e.g. tumour, mass, AVM)
- Primary progressive aphasia

MECHANISM/S

Wernicke's aphasia is caused by a lesion in the posterior superior temporal gyrus of the dominant hemisphere.[226] This region is supplied by branches of the inferior division of the middle cerebral artery (MCA).[47] The most common cause of Wernicke's aphasia is ischaemic infarction of the inferior division of the MCA. Patient hand dominance (i.e., being left- or right-handed) correlates with the side of the dominant cerebral hemisphere and, therefore, has potential localising value (see also 'Hand dominance' in this chapter). Larger lesions may affect the motor and sensory cortex and/or optic pathways, resulting in contralateral motor and sensory findings and contralateral homonymous hemianopia.[46] Associated contralateral homonymous hemianopia is more common in Wernicke's aphasia (receptive aphasia), whereas motor and sensory findings are more common in Broca's aphasia (expressive aphasia).[46] Refer to Table 5.39 for clinical features of Wernicke's aphasia.

SIGN VALUE

Wernicke's aphasia, or receptive aphasia, is a dominant cortical localising sign. Acute-onset aphasia should be considered a sign of stroke until proven otherwise.

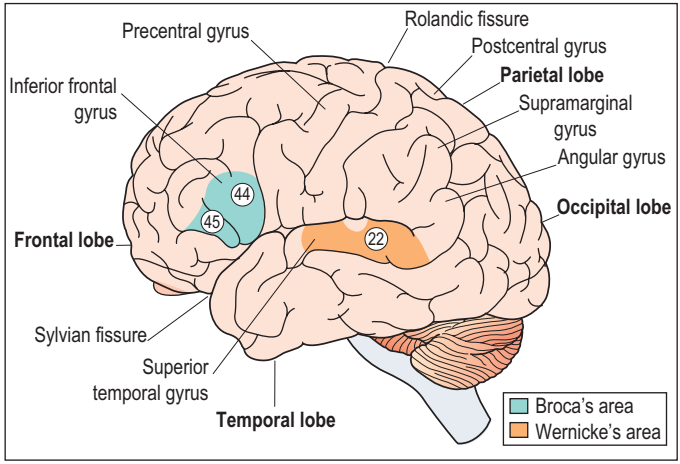


Figure 5.135 Wernicke's area, posterior superior temporal gyrus, dominant hemisphere

22 = Brodmann's area 22; 44 = Brodmann's area 44; 45 = Brodmann's area 45.

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 12A-1.

TABLE 5.39 Clinical features of Wernicke's aphasia

Clinical feature(s)	Abnormality in Wernicke's aphasia
Spontaneous speech	• Fluent, with paraphasic errors • Dysarthria usually absent
Naming	• Impaired (often bizarre paraphasic misnaming)
Comprehension	• Impaired
Repetition	• Impaired
Reading	• Impaired for comprehension and reading aloud
Writing	• Well formed, paragraphic
Associated signs	• Contralateral hemianopia • Contralateral motor and sensory findings less common

Adapted from Kirshner HS, Language and speech disorders: aphasia and aphasiac syndromes. In: Bradley WG, Daroff RB, Fenichel G et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008.

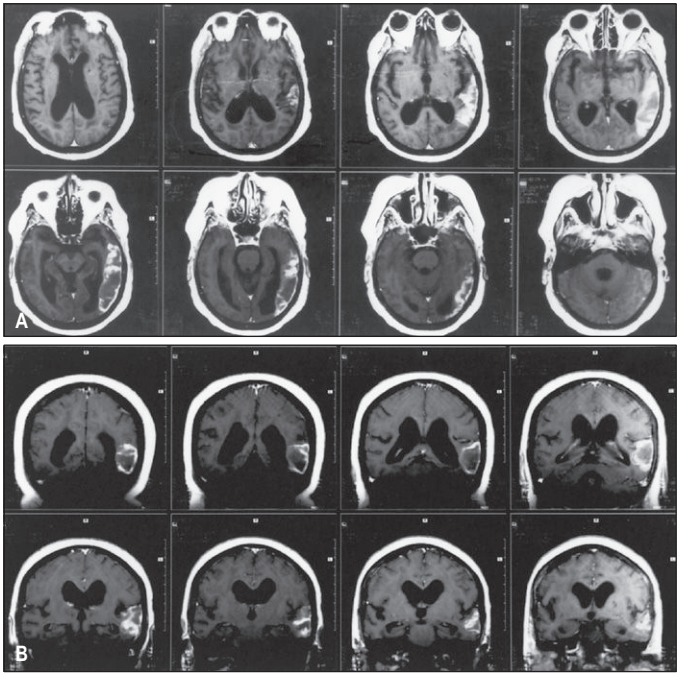


Figure 5.136 MRI of a patient with Wernicke's aphasia caused by a temporal lobe lesion

A, Axial images; **B**, coronal images.

Reproduced, with permission, from Daroff RB, Bradley WG et al, *Neurology in Clinical Practice*, 5th edn, Philadelphia: Butterworth-Heinemann, 2008: Fig 12A-4.

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CHAPTER 6

Gastroenterological Signs

Ascites

Although not strictly a sign, a variety of clinical signs indicate its presence. It is helpful to have an understanding of the underlying mechanism/s of ascites in order to interpret the combination of signs you may elicit when examining a patient.

DESCRIPTION

The pathological accumulation of fluid in the peritoneal cavity.

CONDITION/S ASSOCIATED WITH

As in oedema, variations in oncotic and hydrostatic pressure and vascular wall integrity are central to the development of ascites (see 'Peripheral oedema' in Chapter 3, 'Cardiovascular signs'). All the pathologies that create ascites affect one or more of these factors.

The causes of ascites can be broadly grouped into four categories according to mechanism (Table 6.1).

MECHANISM/S

Peripheral arterial vasodilatation theory

This hypothesis, shown in Figure 6.1, combines two premises: the 'underfill' and 'overflow' theories. The key initiating element in both is *nitric oxide-induced splanchnic vasodilatation.*

- Underfill theory: an imbalance in hydrostatic versus oncotic pressure, which causes the intravascular fluid to leak into the peritoneal cavity.[1] The resulting low blood volume activates the renin–angiotensin–aldosterone (RAA) pathway and the sympathetic nervous system to begin renal sodium and fluid retention, in an attempt to maintain volume.[1] In other words, vascular oncotic pressure is not sufficient to keep fluid in the blood vessels.
- Overflow theory: primary renal sodium retention in patients with cirrhosis causes intravascular hypervolaemia. This increase in intravascular fluid, in turn, causes increased hydrostatic pressure that forces fluid to overflow into the peritoneal cavity.[2]
- Further research following these two theories found that portal hypertension causes the release of nitric oxide and splanchnic bed vasodilatation, which reduces effective arterial blood flow to the kidneys. The RAAS is employed to increase plasma volume, further contributing to fluid overload and ascites.[3–5]

Congestive heart failure, nephrotic syndrome, Budd–Chiari syndrome and myxoedema

People with these conditions are thought to develop ascites because of reduced effective arterial volumes, leading to activation of the RAAS and salt and fluid retention (underfill theory).[3–7]

TABLE 6.1 Causes of ascites

Fluid imbalance (arterial vasodilatation theory)	Exudative
Cirrhosis – common	Exudate-secreting tumours (peritoneal carcinomatosis)
Congestive heart failure – common	Infections (e.g. TB)
Myxoedema	Inflammatory disease (e.g. SLE)
Budd–Chiari syndrome	
Chylous	**Nephrogenic**
Obstruction (e.g. malignant lymphoma)	Haemodialysis
Iatrogenic (e.g. transection of the lymphatics)	Nephrotic syndrome
Retroperitoneal lymph node dissection	

Exudative ascites

Exudative ascites may be caused by:

- increased intraperitoneal oncotic pressure (e.g. peritoneal carcinomatosis causes the tumour cells lining the peritoneum to produce exudates)
- disruption of vessel wall integrity that allows fluid to leak through (e.g. patients with systemic lupus erythematosus can develop an inflammatory serositis leading to exudate).[7,8]

Chylous ascites

Obstruction of lymphatic flow is the main underlying mechanism. This can be due to obstruction raising lymphatic pressures, resulting in fluid being pushed out and/or disrupting vessel integrity leading to leakage. Examples of these two scenarios are malignant lymphoma and surgical rupture of lymph nodes or vessels.[9,10]

Nephrogenic – haemodialysis

The causes of ascites in patients who receive haemodialysis are largely unknown. One possible explanation is uraemia inducing an inflammatory response that causes immune-complex formation and obstruction of lymphatic channels.[11,12]

ASCITES CLINICAL SIGNS

Several clinical signs indicate the presence of ascites but none of them indicate the underlying cause. They are summarised in Table 6.2.

SIGN VALUE

The various signs that are used to detect the presence of ascites have variable sensitivities and specificities (as seen in Table 6.2), but all have value in clinical examination. In patients with abdominal distension, the sign with the best positive likelihood ratio (most likely to have ascites) is the fluid wave (PLR 5.0).[13] The best signs to exclude ascites are absence of oedema (NLR 0.2) and absence of flank dullness (NLR 0.3).[13]

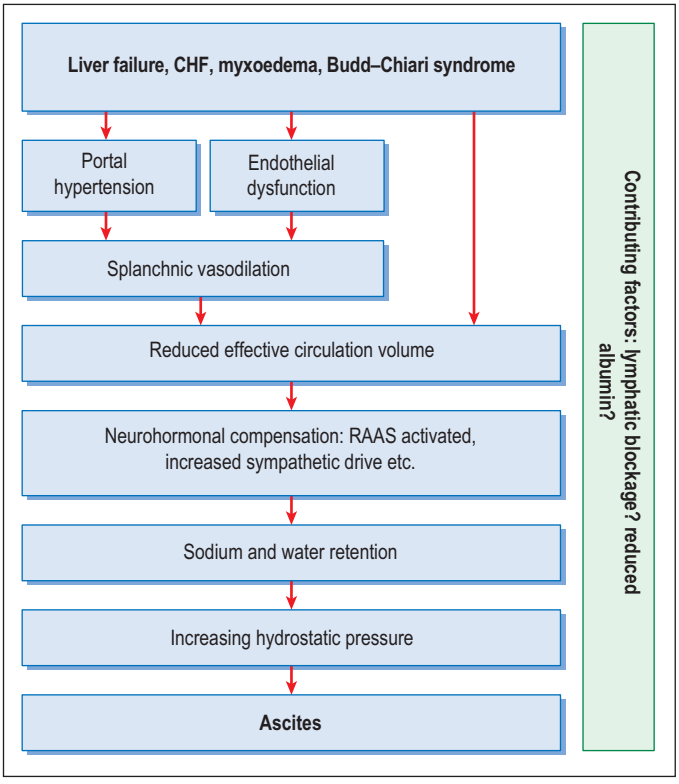

FIGURE 6.1 Mechanisms in the development of ascites

TABLE 6.2 Clinical signs of ascites

Sign	Description	Sensitivity	Specificity	Mechanism of sign
Bulging flanks	Subjective bulging of the flanks	0.78	0.44	Based on the difference in physical properties of water and air and gravity. In ascites, fluid accumulates in the peritoneal cavity and is susceptible to the effects of gravity. Thus, when the patient is lying in the supine position, fluid shifts to the peripheral parts of the abdomen and air moves more centrally. As percussed fluid does not transmit lower frequencies as well as air, the fluid provides a distinct, dull sound compared to the resonant sound of air
Flank dullness	Bilateral dullness to percussion of the abdomen accompanied by tympanic percussion centrally	0.94	0.56	
Fluid wave/ fluid thrill	Percussion on one side of the abdomen transmits a wave of fluid that is felt on the contralateral side	0.50	0.82	
Puddle sign	With the patient resting on knees and elbows, the umbilical area is percussed for dullness to demonstrate fluid accumulation centrally due to gravity	0.51	0.51	
Shifting dullness	With the patient supine, the examiner percusses the abdomen from the umbilicus towards him/ herself. When dullness occurs, the location is noted and the patient is instructed to roll towards the examiner and assume the lateral decubitus position. The noted location is then percussed again and should become tympanic as fluid shifts laterally	0.88	0.56	

Based on Cattaa EL Jr, Benjamin SB, Knuff TE, Castell DO, JAMA 1982; 247: 1165; with permission.

Asterixis (also hepatic flap)

See also 'Asterixis' in Chapter 2, 'Respiratory signs'.

DESCRIPTION

When the patient is asked to hold the arms extended with the hands dorsiflexed, a 'flap' that is brief, rhythmless and of low frequency (3–5 Hz) becomes apparent. Asterixis may be bilateral or unilateral.

CONDITION/S ASSOCIATED WITH

- Liver disease

HEPATIC MECHANISM/S

Little is known about the mechanism of asterixis induced by hepatic encephalopathy. Limited studies have suggested:

- Slowed oscillations in the primary motor cortex cause mini-asterixis, which may or may not be caused by problems in the motor cortex itself.[14]
- Dysfunction of the basal ganglia–thalamocortical loop may be involved.[15]

SIGN VALUE

Asterixis is perhaps more valuable as a marker of severe disease, whatever the aetiology, rather than as a diagnostic tool.[16] One study used asterixis as a predictor of mortality in patients admitted with alcohol liver disease. It found that mortality rate was 56% in those with asterixis compared to 26% in those without.[17]

Bowel sounds

Bowel sounds are thought to occur as food or fluid is pushed through the intestines. As the intestines are hollow, the sounds made echo throughout the abdomen, and are often described as sounding like water through pipes. Bowel sounds may be heard 5–35 times per minute in a healthy person.

SIGN VALUE

The variable amount and timing of bowel sounds makes the sign difficult to interpret and the evidence on their value is scarce and conflicting.

There is minimal evidence that hearing 'normal' bowel sounds argues against bowel obstruction,[13] as most patients with small bowel obstructions will have either hyperactive, diminished or absent bowel sounds.[18]

Bowel sounds: absent

DESCRIPTION

As the name implies, the complete absence of bowel sounds on auscultation. How long one must listen before bowel sounds may be called absent is not clear, with times quoted anywhere from 1–5 minutes.

CONDITION/S ASSOCIATED WITH

More common

- Intestinal obstruction
- Paralytic ileus of any cause, e.g.:
  - Infection
  - Trauma
  - Bowel obstruction
  - Hypokalaemia
  - Vascular ischaemia
  - Side effect to medications

Less common

- Mesenteric ischaemia
- Pseudo-obstruction (Ogilvie syndrome)

GENERAL MECHANISM/S

Absent bowel sounds may be caused by obstruction of an active intestine, resulting in an inability to push food or fluid through, or by an inactive bowel that is not undergoing peristalsis.

Bowel obstruction

In a mechanical obstruction due to any cause (hernia, volvulus, adhesion), the intestines are pushing against a fixed object. The normal oscillatory movement of food and water is not happening (as in a blocked pipe), so no sound is produced. If the obstruction continues, inflammation occurs and, if vascular supply is compromised, normal peristalsis may also stop.

Infection

Although not entirely explained, there is evidence that the lipopolysaccharides (LPS) present on Gram-negative bacteria initiate an inflammatory response in the intestinal smooth muscle layer, which then reduces smooth muscle contractility causing an ileus.[19]

Postoperative ileus

It is hypothesised that manipulation of the small intestine leads to postoperative ileus by promoting *inflammation of the smooth muscle layer*, which then causes a reduction in intestinal smooth muscle activity.[20]

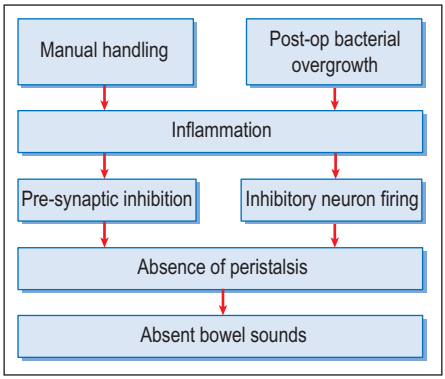

FIGURE 6.2 Possible postoperative ileus mechanism

There is also evidence to suggest that bacterial overgrowth occurs within the gut postoperatively and that the increased presence of bacteria and LPS contributes to inflammation caused by manipulation.[21]

The way inflammation causes ileus is likely to be related to the suppression of synaptic circuits of the enteric plexus, which organise normal propulsion of the instestines.[22] This suppression is caused by pre-synaptic inhibition of enteric motor neurons and/or continuous discharge of inhibitory neurons.

Hypokalaemia

Potassium is needed for normal polarisation and repolarisation of muscle cells. Hypokalaemia causes a *hyperpolarisation* of muscle cells, reducing excitability of the neurons and therefore smooth muscle activity and, thus, leading to ileus.

Pseudo-obstruction

The cause or mechanism of pseudo-obstruction, also known as Ogilvie syndrome, is not clear.

It is thought that an imbalance of autonomic innervation causes a functional bowel obstruction. Normal sacral parasympathetic tone is disrupted, causing an adynamic distal colon. Other studies suggest increased sympathetic tone is the cause – leading to decreased gut motility and sphincter closing. Peristalsis may be absent or impaired.

Bowel sounds: hyperactive (borborygmus)

DESCRIPTION

Frequent, loud gurgling or 'rushing' bowel sounds that sometimes may be clearly heard even without a stethoscope.

CONDITION/S ASSOCIATED WITH:

More common

- Bowel obstruction
- Crohn's disease/ulcerative colitis
- Food hypersensitivity
- Gastroenteritis
- Normal

Less common

- Gastrointestinal haemorrhage

MECHANISM/S

When obstruction is present, the bowel increases peristalsis in an attempt to overcome the blockage.

Bowel sounds: tinkling

DESCRIPTION

High-pitched 'tinkling' sound heard on auscultation of the abdomen that is often described as being like pouring water into an empty glass.

CONDITION/S ASSOCIATED WITH

- Bowel obstruction

MECHANISM/S

Evidence on the mechanism is limited. It is said to signify air or fluid accumulating and striking the bowel under pressure,[23] akin to rain falling on a tin roof.[24]

SIGN VALUE

There is very little evidence on tinkling bowel sounds as a sign.

Caput medusae

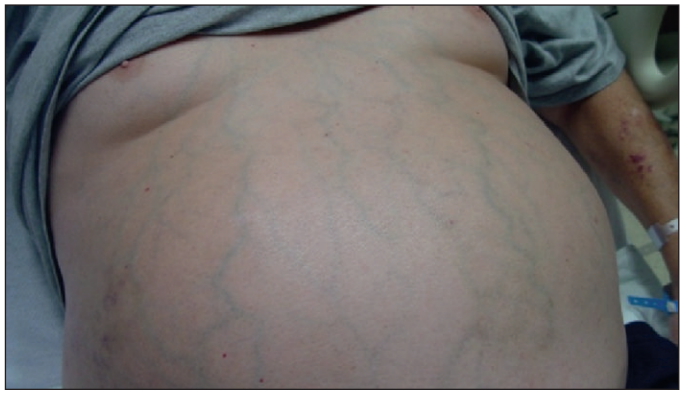

FIGURE 6.3 Caput medusa

Reproduced, with permission, from Saxena R, *Practical Hepatic Pathology: A Diagnostic Approach*, Philadelphia: Saunders, 2011: Fig 6-4.

DESCRIPTION

Dilated veins of the abdominal wall, named after the snakes that made up the hair of the goddess Medusa in Greek mythology.

CONDITION/S ASSOCIATED WITH

Any condition causing portal hypertension, e.g.:

- Cirrhosis of the liver
- Severe heart failure
- Inferior vena cava obstruction

MECHANISM/S

Portal hypertension causes backflow from the portal vein to the para-umbilical veins. The increased pressure and blood volume distend the veins.

SIGN VALUE

Caput medusae is a sign of advanced liver disease and portal hypertension and is rare. Normally, only a few prominent veins may be present. To distinguish between inferior vena cava obstruction and portal hypertension with caput medusa, occlusion of the vein is required.

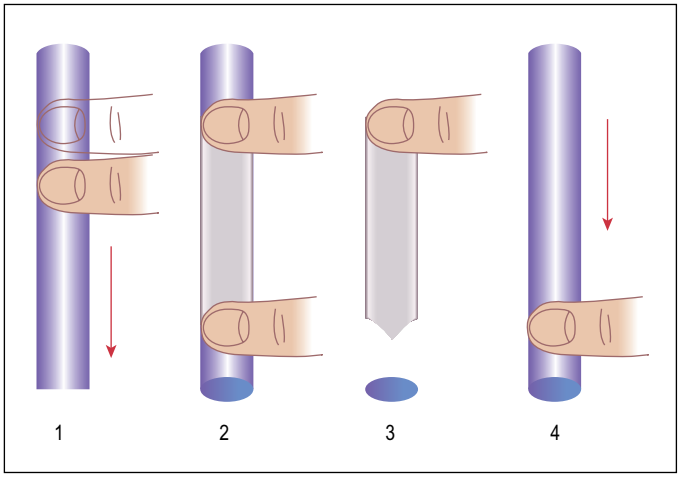

FIGURE 6.4 Measuring flow of a vein

Figuring out which way a prominent abdominal wall vein drains is a necessary skill for the clinician to determine where a blockage in the venous system is.

Measure the flow of the vein below the umbilicus and use the following criteria:

- In severe portal hypertension, flow goes away from the umbilicus towards the feet.
- In inferior vena caval (IVC) obstruction, flow moves towards the head. Abdominal veins distend as they take blood back to the heart, bypassing the blocked IVC.

Based on Talley S, O'Connor NJ, *Clinical Examination: A Systematic Guide to Physical Diagnosis*, 5th edn, Marrickville, NSW: Churchill Livingstone Elsevier, 2006: Fig 5.20.

Cheilitis granulomatosa

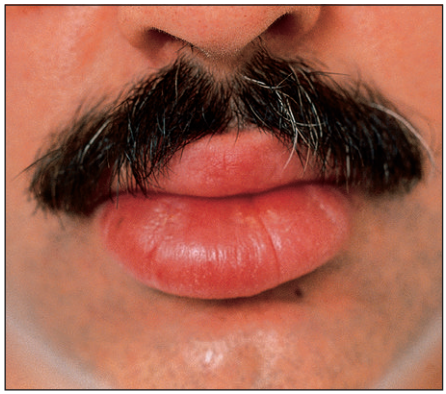

FIGURE 6.5 Cheilitis granulomatosa – diffuse swelling of the bottom lip

Reproduced, with permission, from Bolognia JL, Jorizzo JL, Rapini RP, *Dermatology*, 2nd edn, St Louis: Mosby, 2008: Fig 71-12.

DESCRIPTION

An uncommon painless enlargement of one or both lips. Histologically seen as non-necrotising granulomas with oedema and perivascular lymphocytic infiltration.

CONDITION/S ASSOCIATED WITH

- Crohn's disease – uncommon
- Sarcoidosis
- Melkersson–Rosenthal syndrome – rare

MECHANISM/S

The cause and mechanism are unknown. Once thought to be a localised form of Crohn's disease or sarcoidosis.

SIGN VALUE

Only seen in 0.5% of Crohn's disease patients, and most often after the diagnosis of Crohn's disease. However, some studies still suggest it may be an early manifestation of, or even predispose to, Crohn's disease.[25]

Coffee ground vomiting/bloody vomitus/haematemesis

DESCRIPTION

The vomiting of red blood or 'coffee ground'-like substance or, in the case of haematemesis, coughing of frank red blood.

CONDITION/S ASSOCIATED WITH

- Upper gastrointestinal bleeding[26]

More common

- Peptic ulcer disease
- Gastritis
- Oesophagitis
- Oesophageal varices

Less common

- Mallory–Weiss tear
- Vascular
- Tumour
- Vasculitis

GENERAL MECHANISM/S

Tearing or rupture of a blood vessel within the gastrointestinal tract, regardless of cause or aetiology, can precipitate haemetemesis and/or coffee ground vomitus.

Coffee ground vomits owe their distinctive appearance to blood that has been oxidised by gastric acid. It therefore indicates that the blood and/or bleeding has been present for some time, and potentially is higher up in the gastrointestinal tract, i.e. the duodenum or stomach.

Peptic ulcer disease

Inflammation and erosion of the normal mucosal surface into an underlying artery causes bleeding. Blood irritates the gut and is vomited back up.

Mallory–Weiss tear

Bleeding is due to longitudinal mucosal lacerations at the gastro-oesophageal junction or gastric cardia.

The mechanism behind Mallory–Weiss tears is not completely known. The sudden rise in abdominal/intragastric pressure from vomiting causes an increase in pressure across the gastro-oesophageal junction. This junction is relatively non-compliant and does not distend well with pressure. When the pressure gets high enough or is repeated (with multiple vomits), a mucosal laceration occurs – resulting in bleeding.

Oesophageal varices

In any cause of portal hypertension, the rise in portal vein pressure means blood is directed *away* into lower-pressure systems – collateral systems that include the oesophageal veins, abdominal veins and

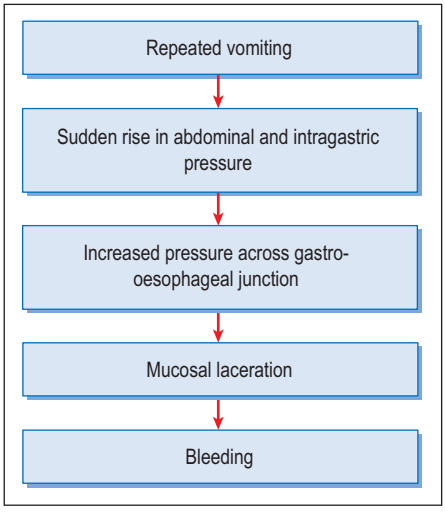

FIGURE 6.6 Mechanism of Mallory–Weiss tear

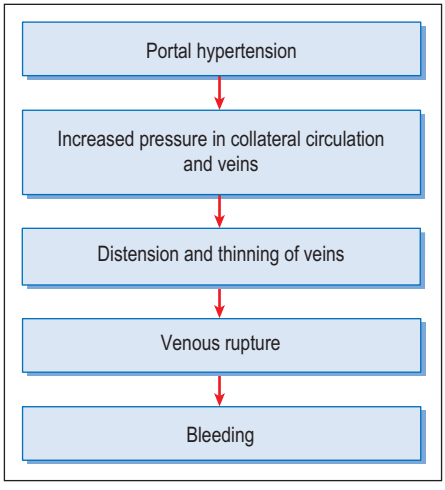

FIGURE 6.7 Mechanisms of haemetemesis in oesophageal varices

rectal veins. These veins become distended, thinner and more fragile. Rupturing of the thin-walled collateral veins/varices in the oesophagus causes pooling of blood and haemetemesis. Gastric varices may also bleed in patients with portal hypertension.

SIGN VALUE

There are a number of causes of upper gastrointestinal bleeding, and other sources of blood coming from the mouth need to be considered (e.g. nose, teeth, sinuses). However, both haemetemesis and melaena are valuable signs and warrant immediate investigation, given the potential for catastrophic bleeding.

Courvoisier's sign

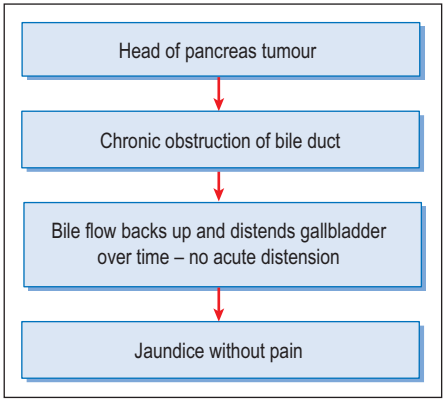

FIGURE 6.8 Possible mechanism of Courvoisier's sign

DESCRIPTION

Taught since 1890, the 'law' is that: in a jaundiced patient the combination of a non-tender, distended gallbladder and obstructive jaundice is generally taken to indicate noncalculous obstruction of the common bile duct.[27]

Despite many interpretations of Courvoisier's original finding, an accepted description is of a palpable, non-tender gallbladder in a patient with jaundice. It is commonly said to be a sign of obstruction to the biliary system by malignancy.

CONDITION/S ASSOCIATED WITH

- Cholangiosarcoma
- Cancer of the head of the pancreas

MECHANISM/S

Dilatation of the gallbladder is the final pathway; however, the exact mechanism that gives rise to a painless, palpable gallbladder is unclear.

One explanation is that *chronic obstruction of the biliary system and/or gallbladder leads to higher biliary duct pressure* over a long period of time and does not provide the acute distension that usually causes inflammation and pain. Malignant causes of obstruction are more likely to provide chronic distension.[28]

For example, a cancer at the head of the pancreas causes sustained, unrelenting obstruction of bile flow, leading to distension of the gallbladder, whereas a gallstone will tend to cause intermittent obstruction with some bile still passing around the stone.

An alternative hypothesis (postulated originally by Courvoisier) is that chronic cholecystitis causes the gallbladder to become fibrotic and shrunken (i.e., it does not distend and therefore cannot cause pain). This has been somewhat demonstrated to be inaccurate.[13]

SIGN VALUE

Given the many interpretations of Courvoisier's sign, evidence can be conflicting. However, assuming that a non-tender gallbladder in a patient with jaundice is the sign elicited, there is good evidence as to its value.

- In detecting obstructed bile ducts, sensitivity of 31%, specificity of 99%, PLR of 26.0!
- In detecting malignant obstruction in patients with obstructive jaundice, sensitivity of 26–55% and specificity of 83–90%.[13]

If present it is a valuable sign.

Cullen's sign

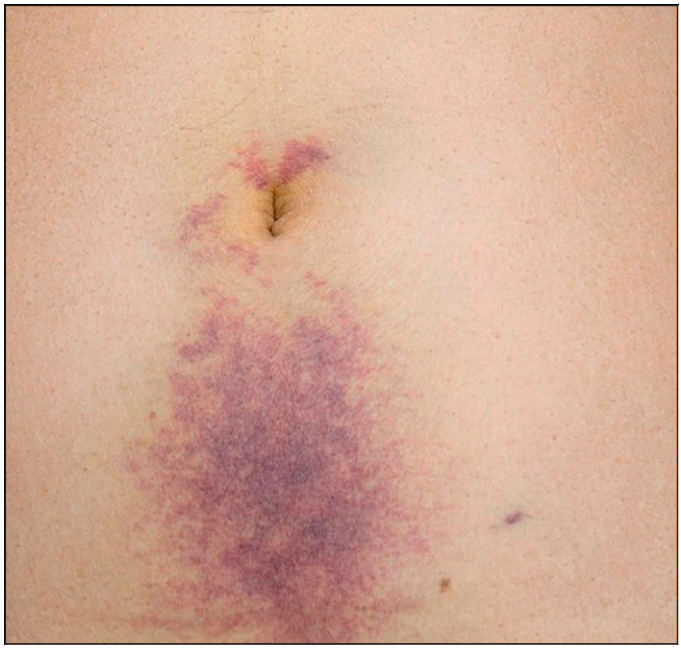

FIGURE 6.9 Cullen's sign

Reproduced, with permission, from Harris S, Naina HVK, Am J Med 2008; 121(8): 683.

DESCRIPTION

Peri-umbilical ecchymoses.

CONDITION/S ASSOCIATED WITH

More common

- Retroperitoneal bleeding
- Post surgery
- Iatrogenic – anticoagulation complication, postoperative
- Rectus sheath haematoma

Less common

- Ectopic pregnancy
- Intrahepatic haemorrhage
- Ischaemic bowel
- Ruptured abdominal aortic aneurysm
- Amoebic liver cyst
- Perforated duodenal ulcer

MECHANISM/S

The final common pathway in most mechanisms is *retroperitoneal bleeding*.

The retroperitoneum is connected to the gastro-hepatic ligament and then to the falciform ligament and finally to the round ligament (the obliterated umbilical vein), which tracks to the abdominal wall around the umbilicus. When a haemorrhage (from any cause) occurs, blood is able to move along these ligaments to the abdominal wall to produce ecchymoses.[29]

SIGN VALUE

Although often still taught as being a sign of pancreatitis, Cullen's sign is very non-specific. In fact, in a study of 770 cases of pancreatitis,[30] only 9 patients exhibited Cullen's sign. Similarly, its association with ectopic pregnancy is now very rare.

It is a relatively specific sign for retroperitoneal bleed so, if seen, it does warrant investigation. However, its absence does not exclude significant underlying pathology.

Erythema nodosum

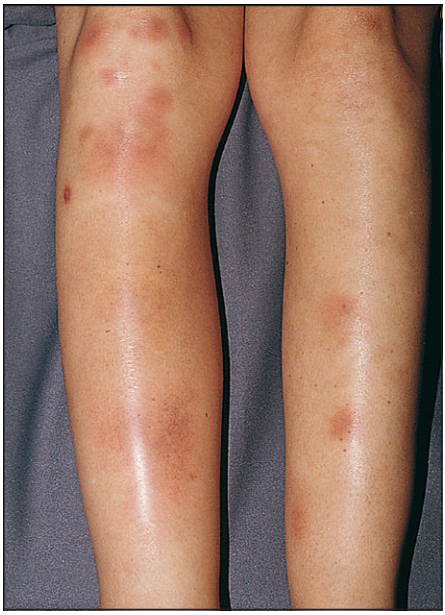

FIGURE 6.10 Erythema nodosum

Reproduced, with permission, from Kliegman RM et al, *Nelson Textbook of Pediatrics*, 18th edn, Philadelphia: Saunders, 2007: Fig 659-2.

DESCRIPTION

A skin disorder of acute-onset eruption of red, tender nodules and plaques predominantly over the lower extremities and, in particular, the extensor surfaces.

CONDITION/S ASSOCIATED WITH

More common[31]

- Inflammatory bowel disease
- Infections
- Sarcoidosis
- Rheumatological disorders
- Drug reactions – especially to sulfonamides and the oral contraceptive pill
- Malignancies
- Pregnancy

MECHANISM/S

The root cause is thought to be a *hypersensitivity reaction* to a variety of stimuli.

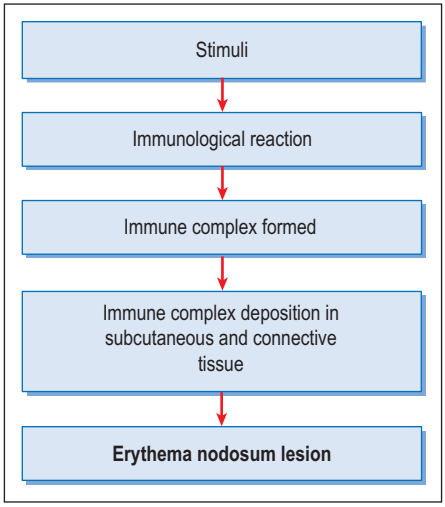

FIGURE 6.11 Erythema nodosum mechanism

The theory is that immune complexes form after exposure to an antigen and are deposited in venules around subcutaneous fat and connective tissue.[31] The subsequent inflammation causes the characteristic lesions. A number of immunological mechanisms have been found to be active:

- Reactive oxidative species have been found at lesion sites.[32]
- Delayed-type hypersensitivity histopathology has been found at mature lesion sites.[33]
- Complement activation has also been implicated.[34]

Why the lesions appear on the shins has not been explained. It has been suggested that a combination of a relatively meagre arterial supply, combined with a venous system that is subject to gravitational effects and has no mechanical pump and an inadequate lymphatic system favour deposition in that area.[35]

SIGN VALUE

Erythema nodosum is not a sensitive or specific sign. However, if found a review of the common causes is often completed. A recent study has found it to be present in approximately 4% of inflammatory bowel disorder patients.[36]

Grey Turner's sign

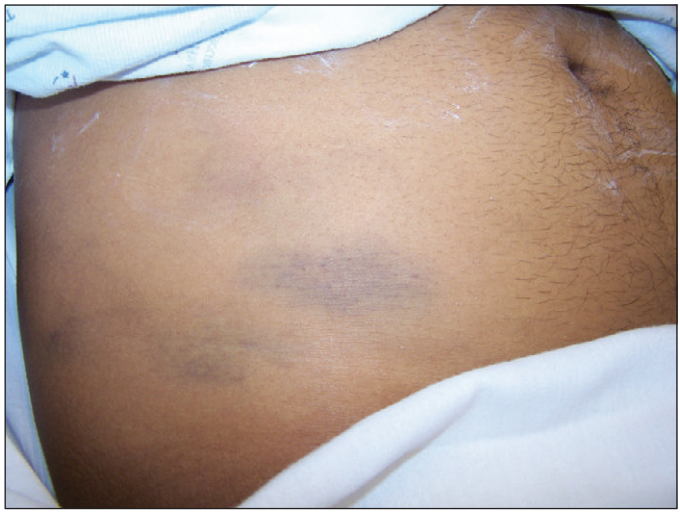

FIGURE 6.12 Grey Turner's sign

Reproduced, with permission, from Feldman M, Friedman LS, Brandt LJ, *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 9th edn, Philadelphia: Saunders, 2010: Fig 58-3.

DESCRIPTION

Ecchymoses or purple discolouration of the flanks.

CONDITION/S ASSOCIATED WITH

- Any cause of retroperitoneal bleed
- Pancreatitis

MECHANISM/S

Basically a hole in the abdominal fascia. A defect in the transversalis fascia allows blood from the posterior pararenal space to move to the abdominal wall musculature and the subcutaneous tissue.[37]

SIGN VALUE

Seen in 14 of 770 patients with pancreatitis,[28] like Cullen's sign it is associated with increased severity of, but is not specific to, pancreatitis. Grey Turner's sign is non-specific but, if seen, the patient should be investigated for potential sources of retroperitoneal bleeding.

Guarding

DESCRIPTION

May be voluntary or involuntary in nature.

Voluntary guarding is the conscious contraction of the abdominal musculature usually in response to fear of pain or anxiety.

Involuntary guarding is discussed under 'Rigidity and involuntary guarding' in this chapter.

CONDITION/S ASSOCIATED WITH

Any cause of peritonism:

- Inflammation of any visceral organ
- Abdominal infection
- Bleeding

MECHANISM/S

In anticipation of pain the patient contracts the abdominal muscles as a protective response.

SIGN VALUE

With a sensitivity of 13–76%, specificity of 56–97% and PLR of 2.6, there is evidence that the finding of guarding is of value in clinical examination.[13]

Gynaecomastia

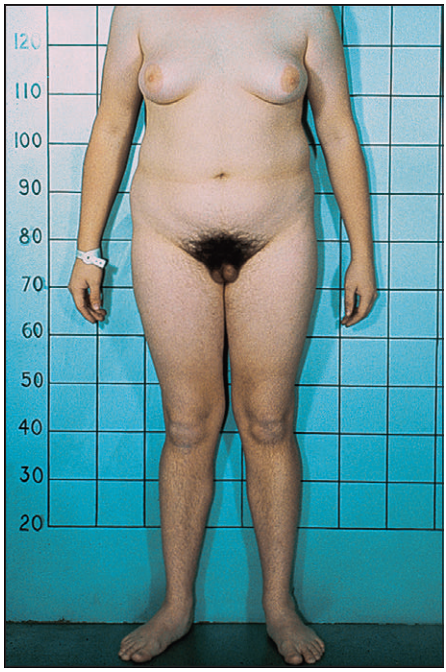

FIGURE 6.13 Gynaecomastia in an adolescent with a congenital form of hypogonadism

Reproduced, with permission, from Wales JKH, Wit JM, Rogol AD, *Pediatric Endocrinology and Growth*, 2nd edn, Philadelphia: Elsevier/Saunders, 2003: 165.

DESCRIPTION

A benign proliferation of glandular tissue, clinically found as a firm disc of tissue underlying the nipple that is 2 cm minimum in diameter. Gynaecomastia usually develops bilaterally. It can be unilateral during the initial stages, becoming bilateral after some months. Only around 10% of cases are unilateral.[38,39]

Gynaecomastia must be differentiated from adipomastia/lipomastia (pseudogynaecomastia), which refers to fat deposition *without* glandular proliferation (i.e., fat rather than true breast tissue).

CONDITION/S ASSOCIATED WITH

More common

- Physiological
- Drugs, commonly:
  - Cimetidine
  - Digitalis
  - Spironolactone
  - Methyldopa
  - Captopril
  - Calcium channel blockers
  - Chemotherapeutic agents
- Radiotherapy
- Hepatic cirrhosis
- Hypogonadism of any cause

Less common

- Hyperthyroidism
- Re-feeding syndrome
- Renal failure and dialysis
- Testicular tumours
- Congenital abnormalities (e.g. Kallmann's syndrome, Klinefelter's syndrome)

GENERAL MECHANISM/S

Gynaecomastia is principally caused by:

1. high levels of circulating oestrogen
2. increases in the oestrogen : testosterone ratio
3. androgen insensitivity.

All of these situations favour increased oestrogen activity in the glandular tissue of the breast, leading to proliferation.

Physiological gynaecomastia

Most often occurs at puberty and middle age.

In males, two important sources of oestrogen production are the testes (via luteinising hormone [LH] and human chorionic gonadotropin [hCG] secretion) and peripheral tissues and fat (via the aromatisation of the androgens to oestrogens).

- At puberty gynaecomastia is believed to be caused by a quicker-than-normal initial rise in oestrogen production.[40–42]
- Older males have decreased testicular function and increased weight and fat storage – this leads to decreased testosterone production from the testes and increased androgen-to-oestrogen aromatisation peripherally.[40]

Drugs

There is increasing recognition of the mechanism/s induced by a number of common drugs. A summary of these is shown in Table 6.3.

Hepatic cirrhosis

In hepatic cirrhosis, the liver's normal metabolic functions are impaired, leading to the *reduced breakdown of androgens*. The increase in circulating androgens results in *increased aromatisation* in the periphery to oestrogens.[44,40]

Hyperthyroidism

Few theories have been suggested for the link between gynaecomastia and hyperthyroidism. There may be increased adrenal androgen production and an increase in the rate of peripheral androgen aromatisation.[41,42]

Hypogonadism

As with ageing testes, primary failure of the testes leads to greater deficits in testosterone production compared to oestrogen – this imbalance may lead to gynaecomastia.

Re-feeding syndrome

It is believed that gonadal function is suppressed during starvation. When re-feeding occurs, the pituitary–adrenal axis is reactivated and increases testicular function. Gynaecomastia occurs as a result, in a very similar way as in puberty.

Renal failure and dialysis

Similar to re-feeding after starvation, testicular function is suppressed during renal failure and then reactivated when the patient commences dialysis. Gynaecomastia is seen 1–7 months after dialysis initiation and usually resolves within a year.[45,46]

Testicular tumours

As described earlier, the Leydig cells of the testes produce both testosterone and oestrogen. Benign Leydig tumours produce an *abnormally high amount of oestrogen* compared to testosterone, and thus may give rise to gynaecomastia.[47]

Tumours that produce hCG also cause gynaecomastia. The increased *levels of hCG stimulate Leydig cells to produce more testosterone and oestrogen*. The testosterone is converted to oestrogen both physiologically in the periphery and pathologically by the tumour itself.[48]

SIGN VALUE

Although a non-specific finding, with up to 65% of pubertal boys and over 60% of 70-year-olds displaying gynaecomastia, it is still a valuable sign,[49,50] especially if it is noted in a patient with other clinical signs. Given that its mechanism is routed via either the gonads or peripheral fat, identifying gynaecomastia enables the underlying pathology to be localised more easily.

TABLE 6.3 Drug-induced gynaecomastia mechanisms

Drug	Mechanism
Spironolactone	Multiple mechanisms:[43] 1 Increased aromatisation of testosterone to oestradiol 2 Decreased testosterone production from testes 3 Displacement of testosterone from steroid binding globulin, causing increased clearance 4 Binds to androgen receptors and prevents testosterone binding
Digoxin	Structurally similar to plant-derived oestrogens – can stimulate oestrogen receptor directly
Histamine 2 receptor blocker (e.g. cimetidine)	Several mechanisms proposed:[43] 1 Blocks androgen receptors, causing increased oestrogen-to-androgen ratio 2 Alters prolactin level – negative feedback on gonadotropin hormone – less LH produced
Proton pump inhibitors	Inhibition of oestradiol metabolism – increases in oestrogen-to-androgen ratio
Anti-androgens (used in prostate cancer therapy or pre-sex change)	Decreased androgens – increased ratio of oestrogen to androgen
Testosterone replacement therapy	Increased testosterone leads to increased aromatisation of testosterone to oestrogen in peripheral tissues LH replacement also favours secretion of oestradiol from the Leydig cells of testes[43]
Calcium channel blockers	Likely to be related to increased levels of prolactin[43]

Hepatic encephalopathy

DESCRIPTION

Hepatic encephalopathy refers to an array of symptoms resulting from acute or chronic liver failure. Forgetfulness, decreased cognitive function, confusion, altered sleep–wake cycle, irritability, asterixis and decreased level of consciousness and even coma have all been reported.

CONDITION/S ASSOCIATED WITH

- Chronic liver failure
- Acute liver failure

MECHANISM/S

Despite large amounts of research, the exact pathogenesis of hepatic encephalopathy has not been agreed upon.

It is thought to be multi-factorial with neurotoxicity, oxidative stress, benzodiazepine-like ligands, astrocyte swelling, gamma-aminobutyric acid (GABA), abnormal histamine and serotonin transmission, and inflammation/oedema all being involved.[51]

Some of the theories are discussed below. Of these, the ammonia theory is the most fully researched hypothesis at present.

Ammonia hypothesis

This is the most studied and currently the most accepted explanation of hepatic encephalopathy. In this theory *decreased breakdown of ammonia* and the presence of *porto-systemic shunts* allow increased levels of ammonia to enter the systemic circulation and go to the brain, where it disrupts normal CNS function. It is proposed that ammonia may do this by the following means:[52]

- Once in the brain increased ammonia levels cause swelling and dysfunction of the astrocytes to the point where they can no longer maintain the environment around the neurons, resulting in neuronal malfunction.
- The increased swelling of the astrocytes may lead to oedema and disturb neurotransmitters.
- Ammonia in high concentrations impairs neuronal transmission in experimental studies.
- Ammonia may alter the gene expression of proteins required for CNS function.

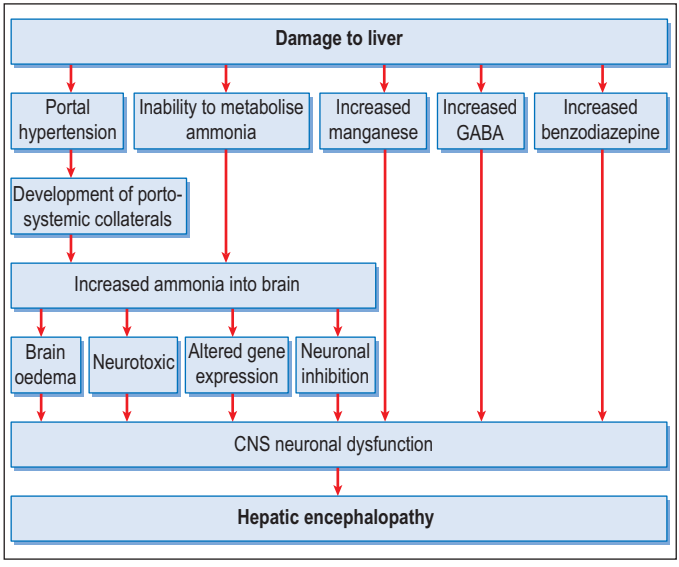

FIGURE 6.14 Mechanism/s involved in hepatic encephalopathy

GABA-ergic hypothesis

In patients with hepatic encephalopathy, *increased levels of GABA* have been found. In this theory increased GABA levels, derived from the gut, result in neuronal function inhibition and hepatic encephalopathy.[53]

Benzodiazepine hypothesis

Increased levels of benzodiazepine-like substances have been reported in the brains of people with hepatic encephalopathy.[54] As in the GABA-ergic hypothesis, this is thought to increase neuronal inhibition.

Manganese hypothesis

Manganese in chronically high levels is known to cause neuronal and basal ganglia damage. It is normally excreted via the hepatobiliary route. In liver failure it is suggested that increased manganese levels damage the CNS and contribute to hepatoencephalopathy.

TNF-α – a unifying theory?

More recently, an all encompassing hypothesis involving tumour necrosis factor (TNF)-α has been proposed.[53] Under this premise it is increased levels of TNF-α that cause neurotoxicity and hepatic encephalopathy. It is suggested that all of the stimuli mentioned previously raise TNF-α levels and thus cause neurotoxicity.

SIGN VALUE

Hepatic encephalopathy is specific to liver disease but needs to be differentiated from other pathologies that may produce a similar set of signs and symptoms. It is seen in 30–45% of patients with liver cirrhosis.[55]

In acute liver failure, the presence of hepatic encephalopathy has negative prognostic value.[56,57] 31% of patients in acute liver failure with encephalopathy required liver transplant or died in one study,[56] and 71% of patients in another study of severely encephalopathic patients had similar outcomes.[57]

Hepatic foetor

DESCRIPTION

A sweet/musty odour smelt on the patient's breath.

CONDITION/S ASSOCIATED WITH

- Hepatic failure

MECHANISM/S

Due to the failing liver's inability to metabolise bacterially degraded methionine and mercaptan dimethyl sulfide, these substances pass through the lungs and are exhaled, producing a distinctive smell.

SIGN VALUE

Although common in hepatic encephalopathy, it is detected infrequently. It can be mistaken for other odours, and therefore can be an inconsistent sign.[58]

Hepatic venous hum

DESCRIPTION

Low-pitched hum heard over the liver when auscultating with the bell of the stethoscope.

CONDITION/S ASSOCIATED WITH

- Portal hypertension
- Large haemangioma
- Hepatoma

MECHANISM/S

A hepatic venous hum occurs with portal hypertension as the blood flows into the lower-pressure systemic system via collateral vessels from the higher-pressure portal system, creating a continuous 'noise'.[59]

Hepatomegaly

DESCRIPTION

An enlarged liver, often taught as being larger than 13 cm in diameter from superior to inferior border.

CONDITION/S ASSOCIATED WITH

There are many potential causes of hepatomegaly. Possible classifications include those given in Table 6.4.

MECHANISM/S

The mechanisms involved in hepatomegaly come down to:

1. increased vascular engorgement
2. inflammation
3. deposition and expansion due to non-liver cells/materials
4. a combination of points 1–3.

Congestive heart failure

In congestive heart failure the back-up of pressure into the venous system owing to ineffective filling or forward outflow leads to a congested and engorged liver.

Infective

Inflammation and swelling of the liver is the principal mechanism in many of the infective pathologies (e.g. hepatitis, malaria, Epstein–Barr virus [EBV]).

Inflammation may also contribute to other non-infective causes of hepatomegaly. Note that in hepatitis the liver may be enlarged or, over time, become scarred and shrink to a smaller size.

Infiltrative

Infiltrative disorders such as sarcoidosis and haemochromatosis lead to deposition of inappropriate material in the liver. The additional material enlarges the liver. Similarly, primary or secondary malignancy enlarges the liver with tumour cells and inflammation.

SIGN VALUE

Percussion of the liver span is highly operator-dependent and does not always provide an accurate estimation of liver size.[13] Studies[60,61] have shown mediocre sensitivity (61–92%) and poor specificity (30–43%) in using percussion to determine the size of the liver.[13] If the liver is felt below the costal margin, it does have 100% specificity and a PLR of 233.7![62]

In summary, percussing for size of the liver does not appear to be accurate. However, if the liver is felt on deep palpation below the costal margin, it is more than likely enlarged.

TABLE 6.4 Causes of hepatomegaly

Infective	Infiltrative	Neoplastic	Metabolic	Vascular
Infective mononucleosis	Sarcoidosis	Hepatocellular carcinoma	Fatty liver	Heart failure
Hepatitis A and B	Haemochromatosis	Tumour metastases	Storage diseases	Budd–Chiari syndrome
Malaria	Amyloidosis	Haemangioma		
Liver cysts		Leukaemia		
Liver abscess		Lymphoma		
		Haematoma		

Jaundice

DESCRIPTION

Yellowing of the skin, sclera and mucous membranes.

CONDITION/S ASSOCIATED WITH

There are many different causes of jaundice; they can be grouped as shown in Table 6.5.

MECHANISM/S

Jaundice is caused by a build-up of *excess bilirubin that is then deposited in the skin and mucous membranes*. Jaundice is not clinically evident until bilirubin exceeds 3 mg/L. Defects along the bilirubin pathway (shown in Figure 6.15) lead to increased bilirubin and jaundice.

Pre-hepatic

See 'Haemolytic/pre-hepatic jaundice' in Chapter 4, 'Haematological/oncological signs'.

Intrahepatic

In intrahepatic jaundice the liver's *ability to take up bilirubin, bind, conjugate and/or secrete it* into the bile canaliculi is impaired. This can be due to either acquired damage to or necrosis of liver cells or genetic deficiencies in the bilirubin pathway.

For example, in Gilbert's syndrome, a genetic abnormality of the enzyme glucuronyltransferase reduces the ability to conjugate bilirubin. As a result, unconjugated bilirubin cannot be excreted properly and hyperbilirubinaemia occurs to a level that eventually causes jaundice.

Similarly, in Dubin–Johnson syndrome a genetic defect in a transporter (cMOAT) does not allow conjugated bilirubin to be secreted effectively, and again bilirubin rises, resulting in jaundice.

Post-hepatic

Post-hepatic jaundice is caused by a *blockage of bile ducts* preventing the excretion of conjugated bilirubin. Bile backs up through the liver into the blood.

TABLE 6.5 Causes of jaundice

Pre-hepatic causes	Hepatic causes	Post-hepatic causes
See Chapter 4, 'Haematological/ Oncological signs'	MORE COMMON	
	Viral hepatitis	
	Cirrhosis of the liver	Gallstones
	Cholestasis	
	Drug-induced	
	LESS COMMON	
	Primary biliary cirrhosis	Pancreatic cancer
	Primary sclerosing cholangitis	Biliary atresia
	Gilbert's syndrome	Cholangiosarcoma
	Crigler–Najjar syndrome	
	Malignancy of the liver	

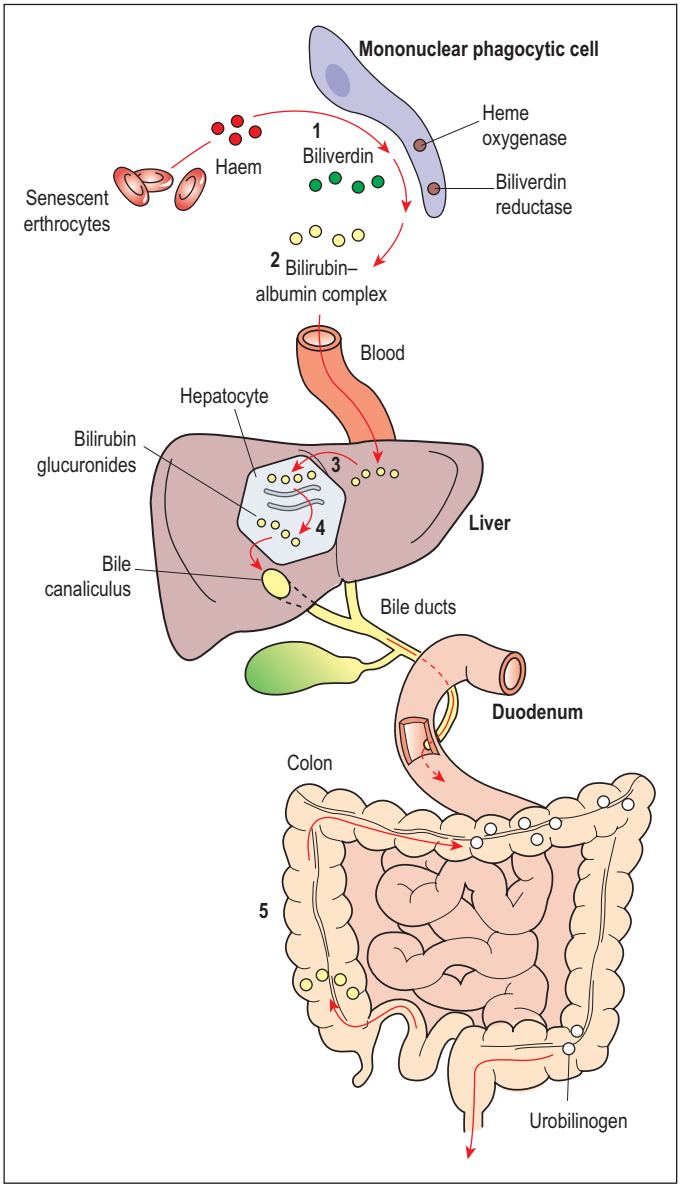

FIGURE 6.15 Bilirubin metabolism and elimination

1 Normal bilirubin production from haem (0.2–0.3 g/day) is derived primarily from the breakdown of senescent circulating erythrocytes.

2 Extrahepatic bilirubin is bound to serum albumin and delivered to the liver.

3 Hepatocellular uptake and **4** glucuronidation in the endoplasmic reticulum generate bilirubin, which is water-soluble and readily excreted into bile.

5 Gut bacteria deconjugate the bilirubin and degrade it to colourless urobilinogens. The urobilinogens and the residue of intact pigments are excreted in the faeces, with some reabsorption and excretion into urine.

Reproduced, with permission, from Kumar V, Abbas AK, Fausto N, Aster JC, *Robbins and Cotran Pathologic Basis of Disease, Professional Edition*, 8th edn, Philadelphia: Saunders, 2009: Fig 18-4.

DARK-COLOURED URINE/PALE-COLOURED STOOLS OF BILIARY OBSTRUCTION

Often associated with post-hepatic or obstructive jaundice is the sign of 'dark urine/pale stools'. In healthy people unconjugated bilirubin is bound tightly to albumin and cannot be excreted in the urine (it cannot 'fit' through the glomerulus of the kidney). However, in patients with obstructive jaundice, conjugated bilirubin binds less tightly to albumin and may be excreted in the urine, giving it a dark colour.

Bile duct obstruction does not allow excretion of bilirubin into the intestines; therefore, the stool does not accumulate the bile pigments that normally make it dark in colour, and the patient will have a noticeably pale bowel motion.

Kayser–Fleischer rings

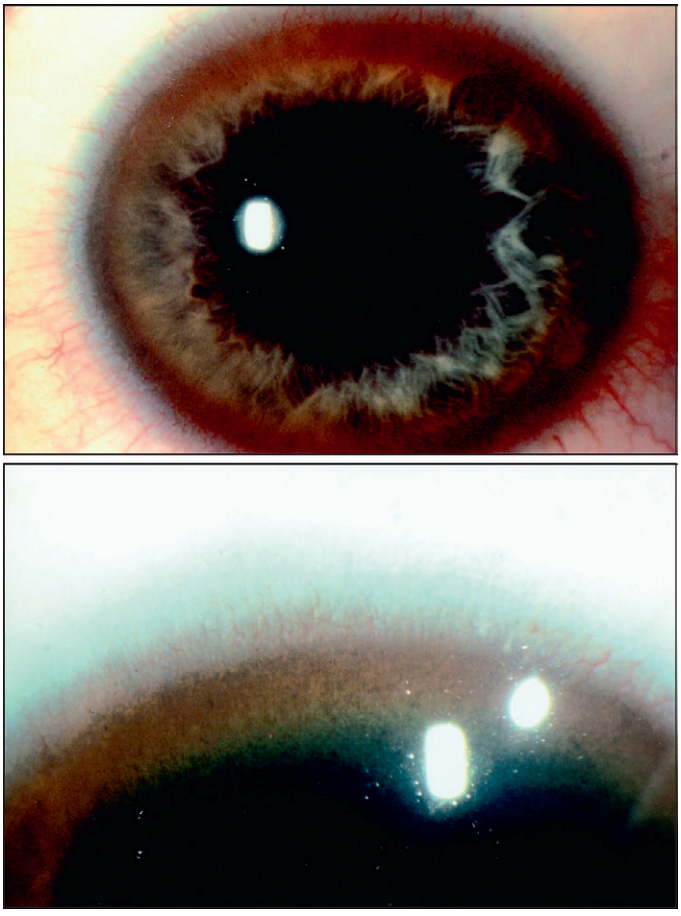

FIGURE 6.16 Kayser–Fleischer rings

Reproduced, with permission, from Liu M, Cohen EJ, Brewer GJ, Laibson PR, Am J Ophthalmol 2002; 133(6): 832–834.

DESCRIPTION

Brown/blue rings at the periphery of the cornea.

CONDITION/S ASSOCIATED WITH

More common

- Wilson's disease

Less common

- Chronic active liver disease
- Primary biliary cirrhosis
- Multiple myeloma

WILSON'S DISEASE MECHANISM/S

Excess copper is the principal cause of this sign.

In Wilson's disease, copper is unable to be excreted into bile, leading to its toxic accumulation in the liver and eventual cellular death of hepatocytes. Copper subsequently leaks into the systemic circulation[63] and copper chelates/granules are deposited in the inner portion of Descemet's membrane in the cornea.[64] The precise mechanism of entry of copper from the systemic circulation into this membrane is controversial. The two main contending theories are that copper is deposited via the limbic system[65,66] or via the aqueous humour.[67]

PRIMARY BILIARY CIRRHOSIS MECHANISM/S

In primary biliary cirrhosis there is reduced biliary tree outflow that causes cholestasis. Copper that would normally be excreted into bile therefore accumulates in the liver, causing hepatotoxicity and leaking into the systemic circulation. As with Wilson's disease, copper is then able to be deposited in other tissues such as cornea.[68]

SIGN VALUE

Kayser–Fleischer rings are present in 99% of patients with concomitant neurological/psychiatric features of Wilson's disease, but in only 30–50% of patients without these features.[69] Therefore, in the absence of neurological/psychiatric features, other differential diagnoses should be considered.

Leuconychia

DESCRIPTION

Complete whitening of the nail plate.

CONDITION/S ASSOCIATED WITH

More common

- Hereditary
- Injury to nail base

Less common

- Hypoalbuminaemia
- Protein-losing enteropathies
- Hepatic cirrhosis
- Chronic renal failure
- Congestive heart failure
- Diabetes mellitus
- Hodgkin's lymphoma

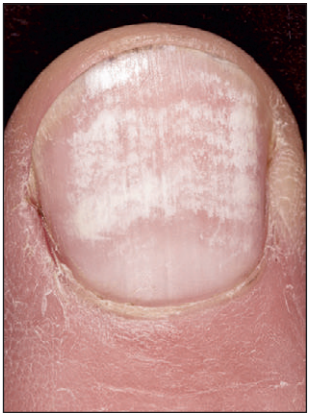

FIGURE 6.17 Leuconychia

Reproduced, with permission, from Habif TP, *Clinical Dermatology*, 5th edn, St Louis: Mosby, 2009: p. 964.

MECHANISM/S

The mechanism is unclear.

In hereditary leuconychia, it is thought that a defect in keratinisation of the cells of the nail plate and underlying matrix is the cause.[70] Instead of cornified cells with keratin forming in the nail matrix, large cells with a substance called keratohyaline are present. Keratohyaline reflects light and does not allow the underlying pink nail bed to be seen.

Liver disease

A form of leuconychia known as 'Terry's nails', where the nail is white proximally and brown distally, has been associated with liver disease, diabetes and congestive heart failure but not with hypoalbuminaemia.

How liver disease leads to this sign is not clear; however, the distal brown portion is thought to be caused by the deposition of melanin.[71]

SIGN VALUE

There is limited evidence on leuconychia's value as a sign and, given its wide array of causes, it is very non-specific. Of interest, Terry's nails is said to be present in 82% of liver cirrhosis patients; however, its significance is unclear.[72]

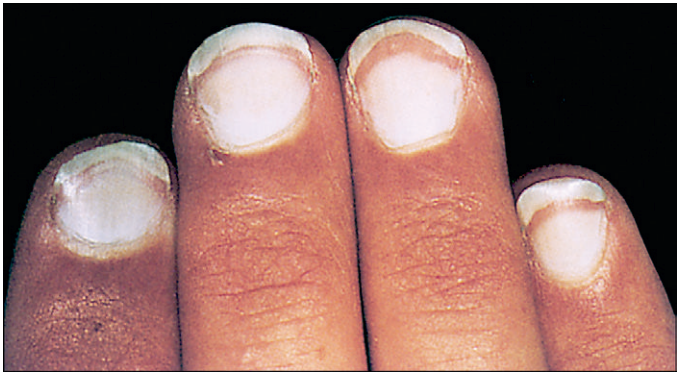

FIGURE 6.18 Terry's nails

Reproduced, with permission, from Habif TP, *Clinical Dermatology*, 5th edn, Philadelphia: Mosby, 2009: Fig 25-44.

Melaena

DESCRIPTION

Black, tarry, offensive-smelling stools.

CONDITION/S ASSOCIATED WITH

- Gastrointestinal haemorrhage/bleed

More common

- Peptic ulcer disease
- Oesophageal varices
- Oesophagitis
- Gastritis

Less common

- Mallory–Weiss tear
- Neoplasm

MECHANISM/S

Bleeding from any cause in the upper gastrointestinal tract. It is often stated that the bleeding must be above the ligament of treitz; however, this is not always the case. The black, foul-smelling nature of the stool is due to the *oxidation of iron from the haemoglobin*, as it descends through the gastrointestinal tract.

SIGN VALUE

If present, melaena demands full investigation, bearing in mind that it is not necessarily specific to the location of the bleed.

Mouth ulcers (aphthous ulcer)

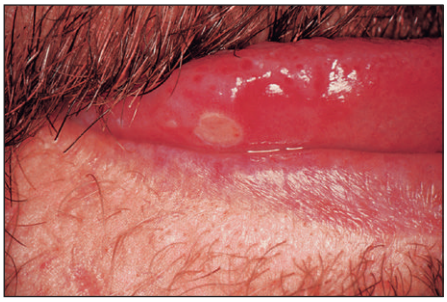

FIGURE 6.19 Mouth ulcer

Reproduced, with permission, from Kanski JJ, *Clinical Diagnosis in Ophthalmology*, 1st edn, Philadelphia: Mosby, 2006: Fig 10-45.

DESCRIPTION

A painful open sore within the oral cavity.

CONDITION/S ASSOCIATED WITH

Numerous associations have been found.

More common

- Trauma
- Stress
- Toothpaste

Less common

- Iron deficiency
- Folate deficiency
- Vitamin B12 deficiency
- Food hypersensitivity
- Humoural/immunological
- Inflammatory bowel disease
- Behçet's disease
- SLE
- HIV/AIDS
- Nicorandil

MECHANISM/S

The mechanism is unknown.

Regardless of the cause, the common appearance is of a breakage of the oral mucosa and infiltration of neutrophils.[73] It is likely that local, systemic, immunological and microbiological processes all play a role.[73,74]

SIGN VALUE

Given at least 10–25% of the population suffers from these ulcers, the value of the ulcers as a single sign is very limited.[75] It needs to be taken into context with other history and symptoms.

Muehrcke's lines

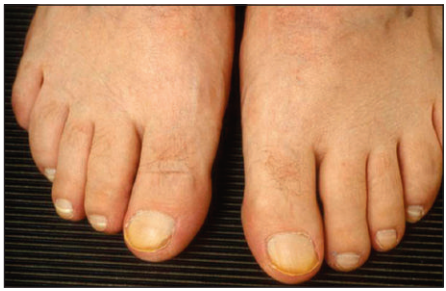

FIGURE 6.20 Muehrcke's lines

Reproduced, with permission, from James WD, Berger TG, Elston DM (eds), *Andrews' Diseases of the Skin: Clinical Dermatology*, 11th edn, Philadelphia: Saunders, 2011: Fig 7.

DESCRIPTION

Two white bands that run parallel to the lunula across the width of the nail. They are smooth and not raised. Normal-appearing pink nail-bed tissue is seen between the two white lines.

CONDITION/S ASSOCIATED WITH

- Hypoalbuminaemia
- Diseases causing serious metabolic stress
- Chemotherapy treatment
- Infection
- Trauma

MECHANISM/S

The specific mechanism for each cause is unclear.

It is suspected to be due to abnormal amounts of stress on the body, *impeding protein formation*. Due to this low protein, oedema within the nail bed compresses underlying blood vessels and blanches the normal erythema of the nail bed, causing the characteristic lines.[76–79]

SIGN VALUE

Limited evidence is available on the value of Muehrcke's sign. It is associated with albumin levels less than 22 g/L[72] and does disappear with correction of albumin deficiency.

Murphy's sign

DESCRIPTION

With the examiner palpating the abdomen below the right subcostal margin, the patient is asked to take a deep breath in and, on doing so, will be caught by sudden pain.

CONDITION/S ASSOCIATED WITH

- Cholecystitis

MECHANISM/S

On deep inspiration the lungs expand, pushing the liver downwards so the inflamed gallbladder is pushed onto the examiner's hand, causing a sudden and unexpected sharp pain.

SIGN VALUE

While individual studies[80–82] have shown sensitivity of 48–87%, specificity of 48–79% and PLR of 1.9 and NLR of 0.6 for Murphy's sign, a systematic review[83] showed a PLR of 2.8 but could not rule out chance (95% CI, 0.8–8.6).

Obturator sign

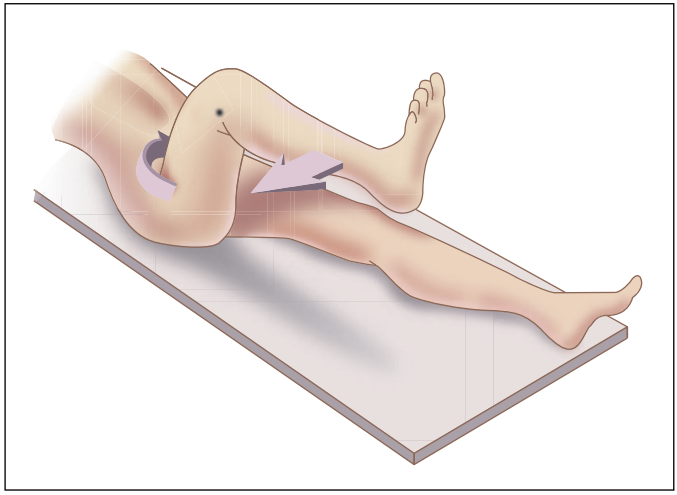

FIGURE 6.21 Eliciting the obturator sign

Reproduced, with permission, from Hardin M, Am Fam Phys 1999; 60(7): 2027–2035.

DESCRIPTION

Pain on internal rotation of the thigh.

CONDITION/S ASSOCIATED WITH

- Appendicitis

MECHANISM/S

The inflamed appendix lies in contact with the obturator internus muscle and, thus, when the leg is rotated, the appendix is stretched and irritated.

SIGN VALUE

The obturator sign, if present, is valuable with a specificity of 94%, but has a sensitivity of only 8%.[84]

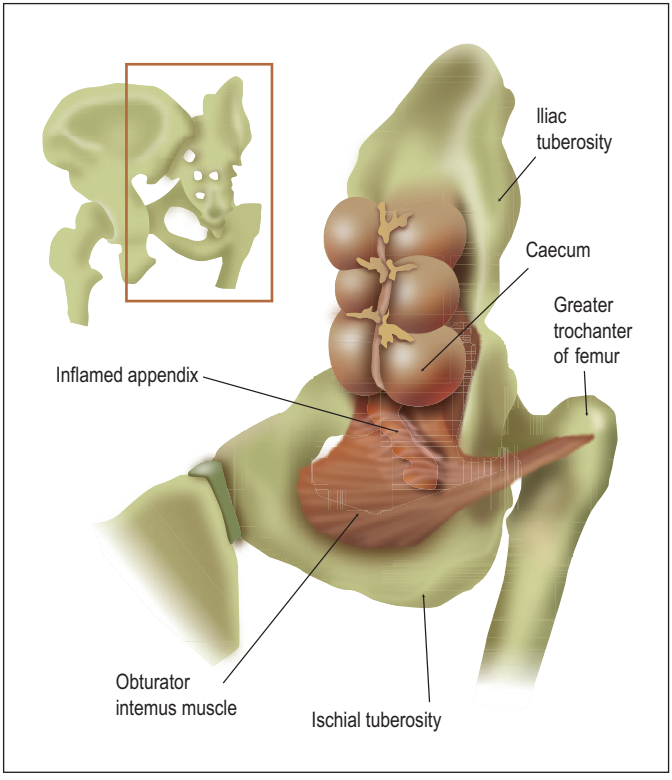

FIGURE 6.22 Anatomy of the obturator sign in appendicitis

Reproduced, with permission, from Hardin M, Am Fam Phys 1999; 60(7): 2027–2035.

Palmar erythema

DESCRIPTION

A symmetrical and slightly warm area of erythema on the thenar and hypothenar eminences of the palm.

- May have a mottled appearance or blanch when pressed.
- Not associated with pain, itch or scaling.
- May involve the palmar aspect of the fingers and proximal nail folds.[85,86]

CONDITION/S ASSOCIATED WITH

Documented in a large number of diseases; most common presentations include:

- Primary causes (where disease of pathological processes cannot be found)
  - Hereditary – rare
  - Pregnancy – common
  - Senile
- Secondary causes
  - Chronic liver disease
  - Autoimmune (e.g. rheumatoid arthritis)
  - Endocrinological – hyperthyroid
  - Neoplastic

GENERAL MECHANISM/S

Regardless of the initial cause, palmar erythema is principally caused by increased perfusion of the palms. Central to many mechanism/s that cause palmar erythema is increased oestrogen levels, increased oestrogen-to-testosterone ratios or raised circulating free oestrogens. Oestrogen has a known proliferative effect on endometrial capillary density, and it is thought that this effect may have a similar effect on the palms.[87]

Other causative factors that may play a role include:

- disordered hepatic metabolism of bradykinin and other vasoactive substances[87]
- abnormal cutaneous vasoconstrictor/vasodilator reflexes.

Pregnancy

Most likely due to increased circulating oestrogens, as discussed under 'General mechanism/s' above, causing alterations in the structure and function of skin and microvasculature.[88]

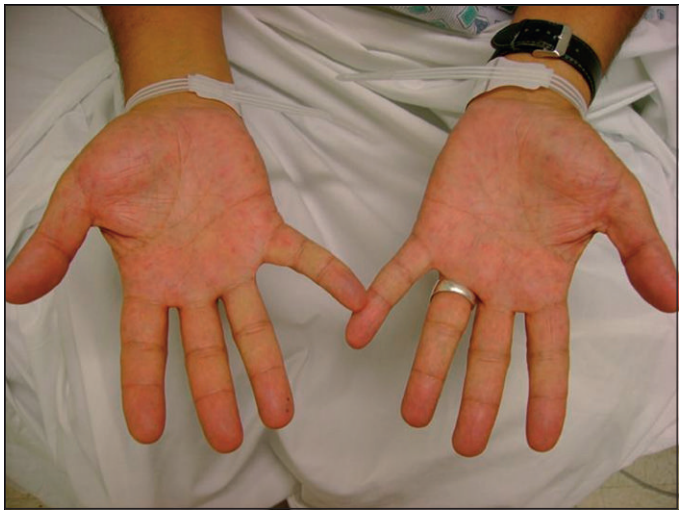

FIGURE 6.23 Palmar erythema in a patient with cirrhosis

Reproduced, with permission, from Goldman L, Ausiello D, *Cecil Medicine*, 23rd edn, Philadelphia: Saunders, 2007: Fig 149-5.

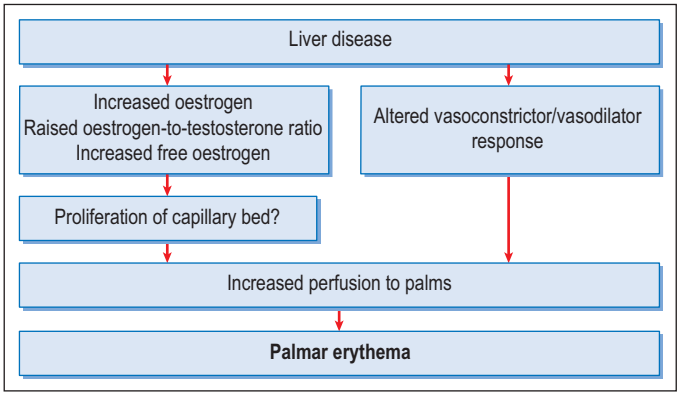

FIGURE 6.24 Mechanism of palmar erythema in liver disease

Chronic liver disease

Increased vascularity of the palms caused by raised circulating levels of oestrogens, oestradiol-to-testosterone ratio or free oestrogen.

An alternative theory or contributing process is that of damaged local autonomic nerves and vasoconstrictor reflexes caused by dysfunction of arteriovenous anastamoses found in cirrhotic patients.[89]

Rheumatoid arthritis

Palmar erythema is a common occurrence in rheumatoid arthritis, with over 60% of patients exhibiting the sign.[90] The pathogenesis remains largely unknown.[91]

Neoplastic

May arise from increased angiogenic factors and oestrogens from solid tumours.[87] In addition, if the liver is involved, raised oestrogen levels may also contribute.

Hyperthyroid

Increased levels of oestradiol-17-beta are seen in some patients with hyperthyroidism and are the likely cause of the development of palmar erythema.[92]

SIGN VALUE

Palmar erythema, although non-specific, does have some value as a sign:

- It has been seen to vary according to the severity of the underlying disease.[87]
- In rheumatoid arthritis it is associated with a more favourable prognosis with fewer digital deformities and higher haemoglobin levels.[87]
- It is a frequent sign of liver cirrhosis, with as many as 23% of ultrasound-proven cirrhosis patients having concurrent palmar erythema.[88]
- It is seen in 15% of patients with primary or metastatic brain malignancies.

Pruritic scratch marks/pruritus

DESCRIPTION

Scratch marks represent a sign related to an underlying symptom (pruritus) that is, in simple terms, the feeling of being itchy. The absence of scratch marks in hard-to-reach places (e.g. between the shoulder blades) when they are present on the rest of the body may be an indication of severity of itch.

CONDITION/S ASSOCIATED WITH

Pruritus is associated with numerous skin conditions and systemic diseases. The systemic diseases that cause pruritus include, but are not limited to, those given in Table 6.6.

GENERAL MECHANISM/S

The skin has many unmyelinated C-fibres that synapse with itch-specific secondary neurons. *It is the irritation of the unmyelinated C-fibres by chemical mediators or 'pruritogens' that causes the sensation of pruritus or itch.*[93]

The main pruritogen is histamine. However, there are numerous others and more are being found each year.

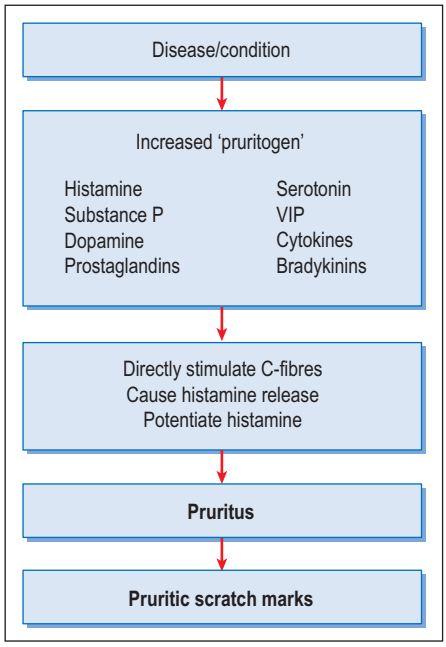

FIGURE 6.25 General mechanism of pruritus

Potential mediators of pruritus are list in Table 6.7.

These factors stimulate pruritus by:

1. directly acting on epidermal nerve endings (e.g. histamine)
2. liberating histamine from mast cells (e.g. neuropeptides)
3. potentiating histamine (e.g. PGE_2, endogenous opioids).

Chronic renal failure

Many factors are thought to contribute to pruritus in chronic renal failure. The accumulation of *pruritogenic factors* due to the kidney's inability to excrete them is thought to be the primary issue. Features seen in chronic renal failure that contribute to pruritus include:[93,94]

- xerosis (dry skin)
- abnormal cutaneous mast cell proliferation
- secondary hyperparathyroidism
- increased pruritogenic cytokines
- increased vitamin A levels
- increased endogenous opioids
- impaired sweating
- peripheral neuropathy
- increased levels of magnesium, stimulating release of histamine
- increased levels of phosphate (cutaneous calcifications stimulating itch receptors).

Hepatobiliary

Like pruritus of chronic renal failure, the mechanism of pruritus in hepatobiliary disorders is thought to be multi-factorial.

Traditional teaching has been that increased bile salts accumulate in blood and tissues inducing pruritus. However, the latest research suggests that, although bile salts may directly or indirectly play a role in pruritus, the evidence for a key role of bile salts in the induction of pruritus in cholestasis is weak.[95] Steroids, steroid metabolites, histamine, serotonin, GABA and cannabinoids are just a few of the pruritogens thought to play a role in the development of itch in cholestasis.

One recent study[96] found that lysophosphatidic acid may cause a rise in intracellular calcium that, in turn, activates itch-inducing nerve fibres in patients with cholestasis.

TABLE 6.6 Causes of pruritus and pruritic scratch marks

Renal	Hepatobiliary	Haematological	Metabolic/ endocrine	Neurological
MORE COMMON				
Chronic renal failure	Infectious hepatitis	Polycythaemia vera	Hyper/hypothyroid	
	Biliary obstruction	Leukaemia/ lymphoma	Diabetes	
LESS COMMON				
	Primary biliary cirrhosis	Iron deficiency anaemia	Multiple endocrine neoplasia (MEN) II	Multiple sclerosis
	Primary sclerosing cholangitis		Carcinoid syndrome	Cerebral tumour
	Drug-induced cholestasis			Stroke

TABLE 6.7 Potential chemical mediators of pruritus

Type of pruritogen	Examples
Amines	Histamine, serotonin, dopamine, adrenaline, noradrenaline, melatonin
Neuropeptides	Substance P, neurotensin, vasoactive intestinal peptide (VIP), somatostatin, α- and β-melanocyte-stimulating hormone (MSH), calcitonin gene-related peptide (CGRP), bradykinin, endothelin, neurokinin A and B, cholecystokinin (CCK), bombesin
Eicosanoids	PGE_1, PGE_2, PGH_2, LTB_4
Cytokines	IL-2, TNF-α and TNF-β, eosinophil products
Opioids	Met-enkephalin, leu-enkephalin, β-endorphin, morphine
Proteolytic enzymes	Tryptases, chymases, kallikrein, papain, carboxypeptidases

Based on Krajnik M, Zylicz Z, Netherlands J Med 2001; 58: 27–40; with permission.

Haematopoieic

The mechanism is unclear.

- Histamine and serotonin have been implicated in the mechanism for polycythaemia vera.[97]
- In Hodgkin's lymphoma some researchers propose histamine as a central mediator,[94] whereas others[98] propose an autoimmune reaction to lymphoma cells inducing the liberation of bradykinins and leucopeptides.

Metabolic and endocrine

The mechanism is unclear.

The hypothesis for the pathogenesis of pruritus in hyperthyroidism is that it is thought to be related to a decrease in the '*itch threshold*' due to the increased body temperature and vasodilatation and activation of the kinin system arising from increased tissue activity and metabolism.[94]

In hypothyroidism, xerosis (dry skin) is the principal cause of itchiness.

Neurological disorders

The mechanism is unclear.

In multiple sclerosis bouts of pruritus are attributed to the activation of artificial synapses between axons in partially demyelinated areas of the CNS.[93]

SIGN VALUE

Little research has been directed towards the value of pruritus as a symptom or sign. Given the wide variety of causes, its specificity is low.

Its prevalence in some of the above conditions is:

- 25–86% in uraemic patients with chronic renal failure[93,99]
- 20–25% in patients with jaundice; prevalent in 100% of primary biliary cirrhosis and a presenting symptom in 50%[100]
- 25–75% in polycythaemia vera[97]
- 4–11% in patients with thyrotoxicosis.[101]

Pruritus may precede the onset of disease by 5 years in Hodgkin's lymphoma.[102]

Psoas sign

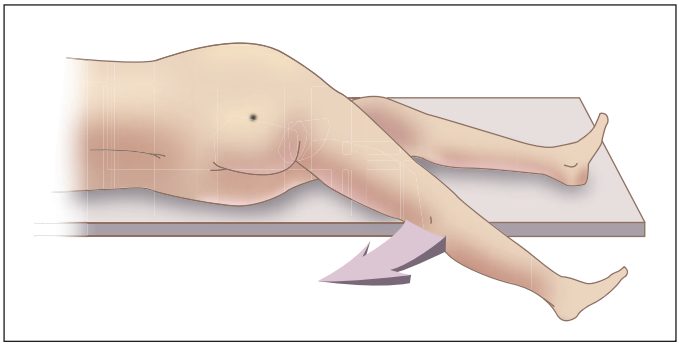

FIGURE 6.26 Psoas sign

Reproduced, with permission, from Hardin M, Am Fam Phys 1999; 60(7): 2027–2035.

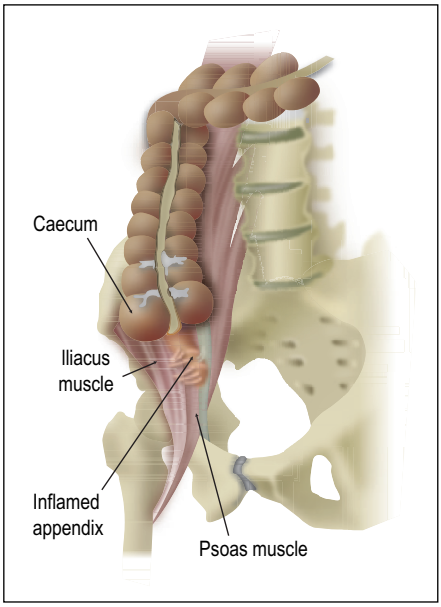

FIGURE 6.27 Psoas sign anatomy

Reproduced, with permission, from Hardin M, Am Fam Phys 1999; 60(7): 2027–2035.

DESCRIPTION

Pain on passive extension of the thigh.

CONDITION/S ASSOCIATED WITH

- Appendicitis
- Psoas abscess

MECHANISM/S

If the appendix is in a retro-caecal position, it may be in contact with the psoas muscle. Therefore, movement of the psoas muscle will move the inflamed appendix, causing pain, with a similar process occurring with a psoas abscess.

SIGN VALUE

Sensitivity of 13–42%, specificity of 79–97%, PLR of 2.0.

Pyoderma gangrenosum

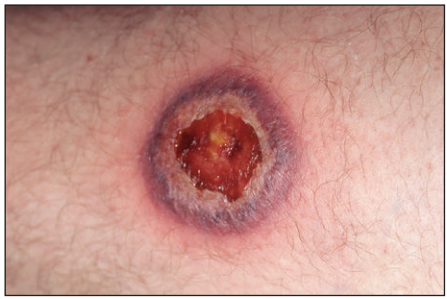

FIGURE 6.28 Pyoderma gangrenosum

Reproduced, with permission, from Weston WL, Lane AT, Morelli JG, *Color Textbook of Pediatric Dermatology*, 4th edn, London: Mosby, 2007: Fig 14-46.

DESCRIPTION

A rare, chronic, often destructive, inflammatory skin disease in which a painful nodule or pustule breaks down to form a progressively enlarging ulcer with a raised, tender, undermined border.[103]

CONDITION/S ASSOCIATED WITH

- Idiopathic: 25–50% of cases
- Inflammatory bowel disease: up to 50% of cases
- Rheumatological disease
- Paraproteinaemia
- Haematological malignancy

MECHANISM/S

The mechanisms of both idiopathic and secondary causes of pyoderma gangrenosum are unclear.

Altered or exaggerated immunological/inflammatory response has been suggested; however, this is only seen in some cases. Given the high incidence of underlying inflammatory bowel disease, cross-reaction between antigens in the bowel and skin causing secondary cutaneous manifestation has also been postulated.[104]

SIGN VALUE

There is little evidence on the value of pyoderma gangrenosum as a sign. However, given its relatively common onset in patients with underlying systemic disease, its presence in an otherwise healthy individual warrants investigation.

Rebound tenderness

DESCRIPTION

The clinician presses down deep on the abdomen and then quickly removes the hand (i.e. the pressure). The patient feels sudden *pain on the release of pressure* rather than the preceding palpation.

CONDITION/S ASSOCIATED WITH

- Any cause of peritonitis

MECHANISM/S

When the abdomen is pushed down and then quickly released, the peritoneum rebounds back and, if inflamed, the rebound movement will activate pain sensory fibres.

SIGN VALUE

Originally said to be one of the cardinal signs of peritonitis; however, recent evidence has found little value as a sign. Studies have shown a wide variation in sensitivity (40–95%) and specificity (20–89%) and PLR 2.0.[13]

Rigidity and involuntary guarding

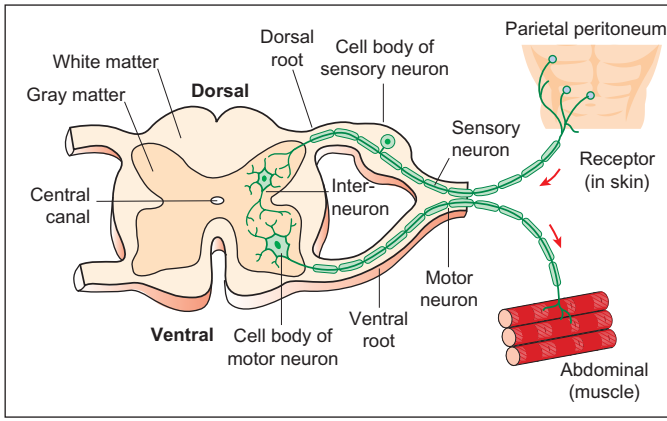

FIGURE 6.29 Example of reflex arc in rigidity/involuntary guarding

DESCRIPTION

The constant involuntary contraction of the abdominal musculature where the abdomen is literally 'rigid' to palpation. There will also be tenderness present.

CONDITION/S ASSOCIATED WITH

- Causes of peritonism

MECHANISM/S

Inflammation of the peritoneum stimulates a *reflex arc* resulting in the contraction of the abdominal muscles.

The parietal peritoneum is innervated by somatic nerve fibres that produce sharp localised pain (unlike the visceral peritoneum). When a pathological process (e.g. appendicitis) occurs and affects or inflames the parietal peritoneum, somatic sensory neurons are stimulated, which travel via the spinal nerves and synapse in the dorsal horn of the spinal cord. Here they then interconnect with a motor neuron in the ventral horn of the spinal cord that stimulates a localised area of abdominal muscle to contract, forming a reflex arc (Figure 6.29). As the initial reflex bypasses the brain, the patient has little control over it and, hence, it is involuntary.

SIGN VALUE

Rigidity, if present, is a valuable sign with a sensitivity of 6–40%, specificity of 86–100% and a PLR of 3.6.[13]

Rovsing's sign

DESCRIPTION

When the left lower quadrant is palpated, pain is felt over the right lower quadrant.

CONDITION/S ASSOCIATED WITH

Traditionally appendicitis; however, in theory inflammation of any organ in the right lower quadrant may elicit Rovsing's sign.

MECHANISM/S

When the left side of the abdomen is palpated, the peritoneum is stretched tight over the inflamed appendix, thus irritating the appendix and peritoneum and localising the pain to the right lower quadrant.

SIGN VALUE

Sensitivity of 22–68% and specificity of 58–96%, PLR of 2.5 and NLR of 0.7.[13]

Scleral icterus

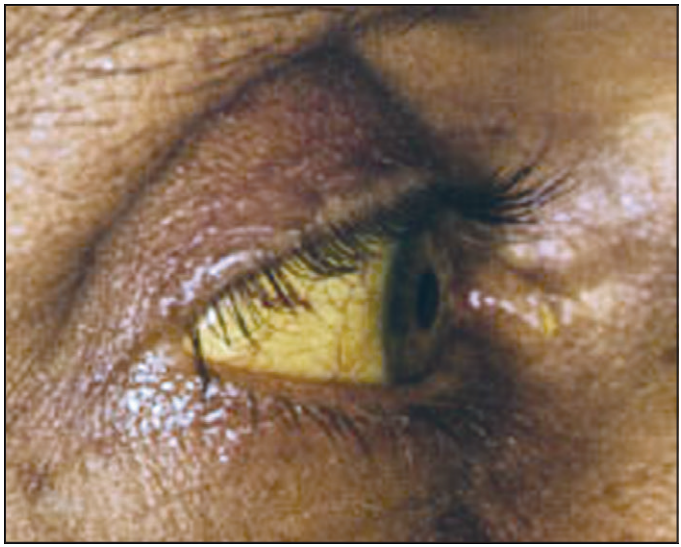

FIGURE 6.30 Scleral icterus

Reproduced, with permission, from Stern TA, Rosenbaum JF, Fava M, Biederman J, Rauch SL, *Massachusetts General Hospital Comprehensive Clinical Psychiatry*, 1st edn, Philadelphia: Mosby, 2008: Fig 21-17.

DESCRIPTION

Yellow discolouration of the sclera.

CONDITION/S ASSOCIATED WITH

See 'Jaundice' in this chapter.

MECHANISM/S

For full details see 'Jaundice' in this chapter. Hyperbilirubinaemia leads to bilirubin deposition in the sclera.

SIGN VALUE

The difficulty in scleral icterus as a sign lies in the ability of the examiner to notice it! In one study,[105] 58% of examiners detected scleral icterus in patients with total serum bilirubin of 2.5 mg/dL, whereas 68% of examiners detected scleral icterus in patients with total serum bilirubin of 3.1 mg/dL.

Sialadenosis

DESCRIPTION

A persistent enlargement of the parotid gland (and occasionally submandibular salivary glands). It is neither inflammatory nor neoplastic in origin. Clinically, sialadenosis is palpable as a soft, bilateral, symmetrical and non-tender enlargement of the parotid glands.

CONDITION/S ASSOCIATED WITH

- Diabetes mellitus
- Malnutrition
- Alcoholism

ALCOHOLISM MECHANISM/S

There is controversy surrounding the precise origin of sialadenosis in chronic alcoholism. Cellular hypertrophy and disturbed fat metabolism are the two main causes proposed. The former involves autonomic nerve dysregulation and, thus, accumulation of intracellular zymogen (a precursor to amylase) granules, either via increased production or reduced secretion from the cell. Zymogen excess leads to cellular hypertrophy. Fatty infiltration has also been implicated, particularly in the later stages.[106–108]

SIGN VALUE

Sialadenosis is a valuable indicator of possible chronic liver disease, as it occurs in 30–80% of alcoholic patients with cirrhosis.[109]

Sister Mary Joseph nodule

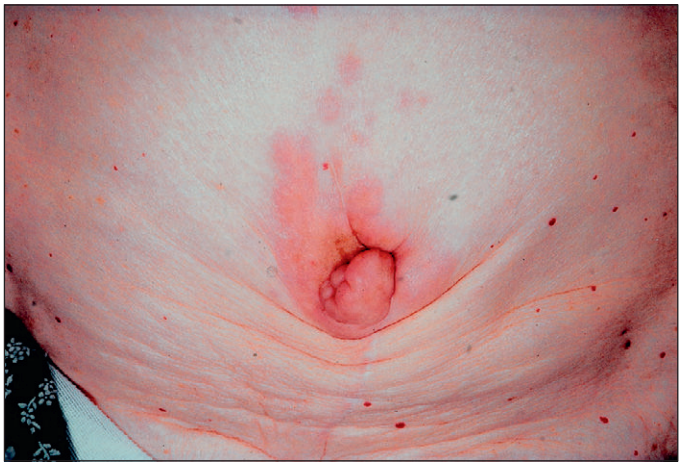

FIGURE 6.31 Periumbilical nodule and erythema – Sister Mary Joseph nodule

Reproduced, with permission, from Brenner S, Tamir E, Maharshak N, Shapira J, Clinics Dermatol 2001; 19(3): 290–297.

DESCRIPTION

A hard, metastatic tumour nodule located at the umbilicus.

CONDITION/S ASSOCIATED WITH

- Adenocarcinoma of abdominal organs, including:
  - Stomach
  - Large bowel
  - Pancreas
  - Ovary
  - Colorectal

MECHANISM/S

It is possible that the vascular and lymphatic systems provide the conduit to the umbilicus. *Direct spread* from the peritoneum is thought to be the most common route for the metastases and nodule.

SIGN VALUE

There are few studies on the sensitivity and specificity of this sign. However, if seen, the Sister Mary Joseph nodule has a negative prognostic value with most patients dying within a few months of diagnosis.[110,111]

Spider naevus

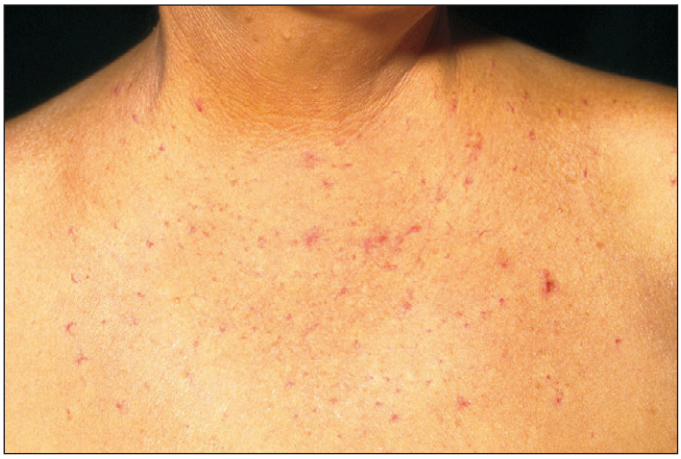

FIGURE 6.32 Spider naevi

Reproduced, with permission, from Talley NJ, O'Connor S, *Clinical Examination*, 6th edn, Sydney: Churchill Livingstone, 2009: Fig 6-10.

DESCRIPTION

Skin lesion consisting of a central arteriole with thread-like vessels that resemble spider's legs radiating outward. Blanching occurs when the spider naevus is compressed, and refilling occurs from the central arteriole outwards when released. Naevi can vary in size from pinhead to 5 mm in diameter.[112]

CONDITION/S ASSOCIATED WITH

More common

- 10–15% of healthy adults and young children
- Alcoholic liver disease
- Hepatitis B and C
- Pregnancy
- Patients on oral contraceptive pill (OCP) and oestrogen products

Less common

- Thyrotoxicosis

MECHANISM/S

Evidence regarding the pathophysiology is severely lacking. Of the few studies in this area, increased plasma oestrogen and substance P have been implicated in vasodilatation and neovascularisation to form spider naevi.[113] Furthermore, the ratio of serum oestradiol to free testosterone is raised in male cirrhotic patients compared to the general population.[114]

SIGN VALUE

The presence of spider naevi is an important tool in predicting the level of liver cirrhosis.

A study by Romagnuolo et al used the presence of spider naevi, platelet count, the presence of splenomegaly and albumin level as variables to calculate the likelihood ratio of cirrhosis/fibrosis.[115] This study found:

- The presence of spider naevi was significantly associated with moderate to severe inflammation, significant fibrosis and cirrhosis of the liver.
- The presence of spider naevi and elevated ferritin was a good predictor of inflammation.
- Spider naevi with either splenomegaly or thrombocytopenia were good predictors of fibrosis.

Splenomegaly

DESCRIPTION

The 'gold standard' definition of splenomegaly is splenic weight (e.g. post-splenectomy) of 50–250 g, decreasing with age.[116] In practice, splenomegaly is commonly detected through palpation of the abdomen during physical examination and/or by radiological means such as ultrasonography.

CONDITION/S ASSOCIATED WITH

There are a multitude of different organ systems and pathological processes that may give rise to splenomegaly. Table 6.8 summarises the possible aetiologies.[117]

MECHANISM/S

The mechanism/s for most causes of splenomegaly can be broken down into the following:

1. increased or excessive immunological response causing hypertrophy
2. hypertrophy in response to increased red cell destruction
3. congestive engorgement in response to increased pooling of blood
4. primary myeloproliferative disorders
5. infiltrative disorders depositing non-splenic material within the spleen
6. neoplastic disorders.

Hypertrophy from immunological response

Associated with infectious mononucleosis, bacterial endocarditis, CMV and HIV and other infections. In times when there is an increased immunological response, the *spleen increases in size and function to accommodate additional white cell proliferation/maturation*.

Increased red blood cell destruction

E.g. hereditary spherocytosis, G6PD, beta-thalassaemia.

In increased red blood cell destruction, there is increased immunological activity in maturing lymphocytes to attack the red blood cells, leading to hypertrophy. Further, in order to cope with the increased destruction of red blood cells, hyperplasia of the splenic sinus cells occurs.[118]

Congestive engorgement

Regardless of the cause of portal hypertension, when it occurs increased blood 'backs up' into downstream vessels including the splenic vein and spleen. With increased portal hypertension and pooling of blood back into the spleen, engorgement and hypersplenism occur.

There is also evidence that impaired venous return leads to increased intra-splenic destruction of red blood cells and increased phagocytic cell activity in the spleen, contributing to hypersplenism.[119]

Myeloproliferative disorders

A number of factors contribute to enlarged spleens in myeloproliferative disorders:[119–122]

1. an increase in pooling of red blood cells in the spleen
2. additional splenic vascularity
3. increased cellularity in the spleen
4. reticular element expansion
5. expansion of lymphoid components of the spleen.

The factors that contribute to the increase in splenic size are dependent, to some extent, on the lineage of the cells proliferating. In one study[122] of patients with primary proliferative polycythaemia (polycythaemia vera), the increase in spleen size was attributed mainly to the increase in splenic vascularity; in myelofibrosis and in hairy cell leukaemia, the increase in spleen size was associated with an increase in both splenic vascularity and cellularity; whereas in chronic granulocytic leukaemia (CGL) and CLL, the increase was attributed more to cellularity than to vascularity.

SIGN VALUE

Although sometimes difficult to palpate, if the spleen is definitely felt it is strongly associated with splenomegaly, with a sensitivity of 18–78%, specificity of 89–99% and PLR of 8.5.[13]

TABLE 6.8 Diseases causing splenomegaly

Category	Group	Examples
Infection	Acute	Infectious mononucleosis, viral hepatitis, septicaemia, typhoid, cytomegalovirus (CMV), toxoplasmosis
	Subacute/chronic	Tuberculosis, subacute bacterial endocarditis, brucellosis, syphilis, HIV
	Tropical/parasitic	Malaria, leishmaniasis, schistosomiasis
Haematological	Myeloproliferative	Myelofibrosis, chronic myeloid leukaemia (CML), polycythaemia vera, essential thrombocytosis
	Lymphoma	Non-Hodgkin lymphoma (NHL), Hodgkin lymphoma
	Leukaemia	Acute leukaemia, chronic lymphocytic leukaemia (CLL), hairy cell leukaemia, prolymphocytic leukaemia
	Congenital	Hereditary spherocytosis, thalassaemia, HbSC disease
	Others	Autoimmune haemolysis, megaloblastic anaemia
Congestive		Cirrhosis, splenic/portal/hepatic vein thrombosis or obstruction, congestive cardiac failure
Inflammatory	Collagen diseases	SLE, rheumatoid arthritis (Felty's)
	Granulomatous	Sarcoidosis
Neoplastic		Haemangioma, metastases (lung, breast carcinoma, melanoma)
Infiltrative		Gaucher's disease, amyloidosis
Miscellaneous		Cysts

Based on Pozo AL, Godfrey EM, Bowles KM, Blood Rev 2009; 23(3): 105–111; with permission.

Steatorrhoea

DESCRIPTION

Stools that are foul-smelling, soapy, bulky and oily in appearance. Quantitatively defined as stool fat >7 g/d. Patients may additionally describes the faeces as difficult to flush down the toilet and very foul-smelling.

CONDITION/S ASSOCIATED WITH

- Typically, malabsorption syndromes including, but not limited to:

More common

- Thyrotoxicosis
- Coeliac disease
- Inflammatory bowel disease
- Drugs (e.g. lipase inhibitors)
- Alteration of anatomy of upper GI tract post surgery
- Cirrhosis of the liver
- *Giardia lamblia* infection

Less common

- Blocked bile ducts
- Lymphatic obstruction
- Whipple's disease
- Biliary tree disease (e.g. primary sclerosing cholangitis, primary biliary cirrhosis)

MECHANISM/S

An inability *to break down* (***luminal***), *absorb* (***mucosal***) *or transport* (***post-absorptive/lymphatic***) fats is the principal cause of steatorrhoea. The increased fat load in the stool causes diarrhoea via an osmotic effect.

Pancreatic insufficiency (luminal)

When >90% of pancreatic function is lost, the normal enzymes that break down fats in the intestinal lumen (e.g. pancreatic lipase) are not produced in sufficient quantities, fats are unable to be broken down and, therefore, cannot be absorbed.

Cirrhosis and biliary obstruction (luminal)

In cirrhosis, insufficient bile acids are produced by the liver to break fats down. Similarly, in biliary obstruction, bile is unable to be secreted into the intestine; therefore, fats are not metabolised and, as a result, they are excreted in the stool.

Coeliac disease (mucosal)

Damage to the intestinal mucosa prevents the normal absorption of micelles. More fat and lipids are left in the intestine and are excreted.

Lymphatic obstruction (post-absorptive)

In rare congenital disorders (e.g. congenital intestinal lymphaniectasia) or after trauma, the lymphatic system may become blocked or compromised. The reassembled lipids are blocked from being transported away from the bowel and, therefore, stay in the bowel and are excreted in the stool.

Striae

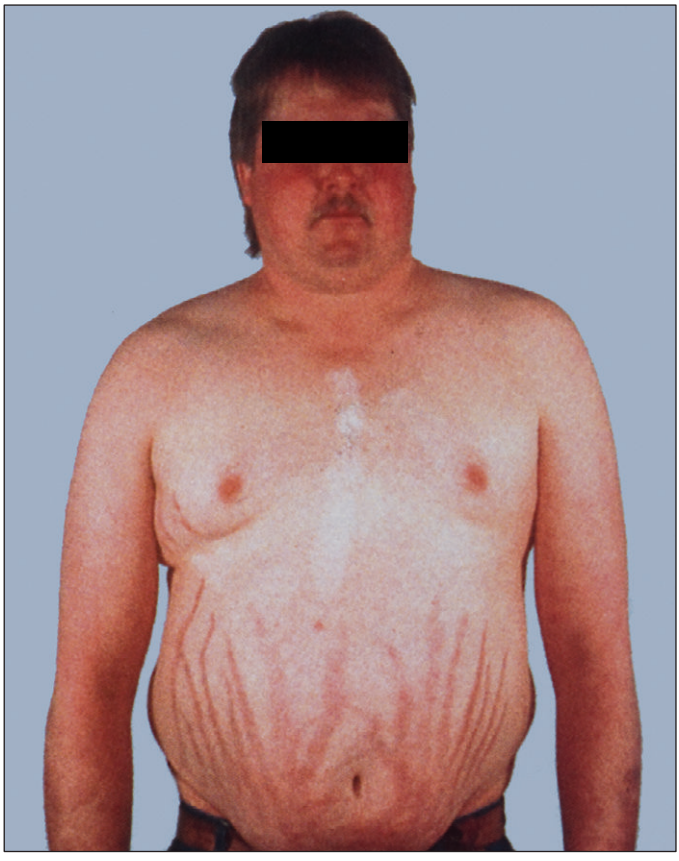

FIGURE 6.33 Abdominal striae

(Also note moon facies and central adiposity.) This patient had Cushing's syndrome.

Reproduced, with permission, from Kumar V, Abbas AK, Fausto N, Aster JC, *Robbins and Cotran Pathologic Basis of Disease, Professional Edition*, 8th edn, Philadelphia: Saunders, 2009: Fig 24-43.

DESCRIPTION

Irregular areas of skin with bluish/purple bands or stripes. The colour of striae may change over time and fade.

CONDITION/S ASSOCIATED WITH

- Obesity and weight gain
- Cushing's syndrome
- Pregnancy
- Puberty
- Steroid therapy

MECHANISM/S

The mechanism of striae is still not clear. Several theories have been proposed for its pathogenesis:

- infection leading to the release of striatoxin that damages the tissues in a microbial toxic way[123]
- mechanical effect of stretching, which is proposed to lead to rupture of the connective tissue framework (e.g. pregnancy, obesity, weight lifting)[124]
- normal growth, as seen in adolescence and the pubertal spurt, that leads to increases in the sizes of particular body regions.[125]

Cushing's syndrome

In Cushing's syndrome, there is an increase in body hormones that are thought to have a *catabolic effect on fibroblasts*, which are required to form the collagen and elastin needed to keep skin taut, leading to dermal and epidermal tearing.[126]

Uveitis/iritis

DESCRIPTION

The uveal tract is comprised of the iris, ciliary body and choroids. When this area becomes inflamed and reddened, it is described as uveitis. If only the iris becomes inflamed, it is simply iritis.

CONDITION/S ASSOCIATED WITH

More common

- Eye trauma
- Infection

Less common

- Inflammatory bowel disease (IBD)
- Vasculitis

GENERAL MECHANISM/S

The pathogenesis of uveitis is poorly understood.

Trauma

- Initially, the mechanism in trauma was thought to be due to foreign antigens becoming sequestered in the uvea.
- Recently, it has been suggested that *microbiological contamination (which accompanies the trauma) and foreign antigens and necrotic products promote pro-inflammatory processes.* Inflammation then causes reddening of the eye.[127]

Infection

Molecular mimicry and non-antigen-specific stimulation of the immune response are the two mechanism/s of uveitis in infection.[127]

In molecular mimicry, self antigens cross-react with pathogens. The immune system then mounts a response against the self antigen, thinking that it is foreign, resulting in inflammation.

It is also thought that the innate immune system may recognise microbial products such as endotoxin, ligands and RNA. If these are located in the eye, they will stimulate inflammation.

Inflammatory bowel disease

No clear mechanism.

It is likely that uveitis in IBD requires a genetic predisposition and an abnormal immune response that damages the respective tissues.[128] Studies[129] have found associations of uveitis with HLA-B27, -B58 and -DRB1*0103. Why, and what triggers the actual inflammation, is still being investigated.

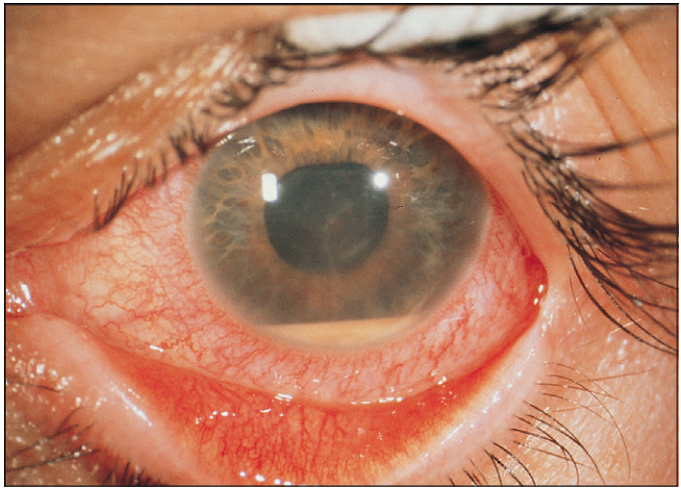

FIGURE 6.34 Severe anterior uveitis associated with HLA-B27

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, St Louis: Mosby, 2008: Fig 7-32.

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CHAPTER 7

Endocrinological Signs

Acanthosis nigricans (AN)

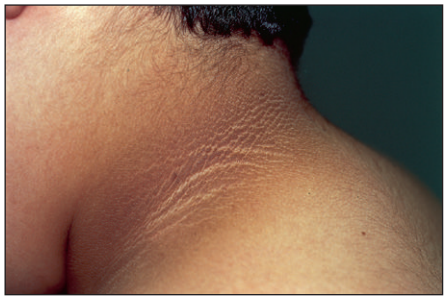

FIGURE 7.1 Acanthosis nigricans

Reproduced, with permission, from Weston WL, Lane AT, Morelli JG, *Color Textbook of Pediatric Dermatology*, 4th edn, London: Mosby, 2007: Fig 17-62.

DESCRIPTION

A grey-black, papillomatous thickening of the skin at the flexor areas. It is usually, symmetrical and velvety to the touch. Acanthosis nigricans (AN) is found most commonly around the posterolateral neck, axillae, groin and abdominal folds.

CONDITION/S ASSOCIATED WITH

More common

- Type 2 diabetes
- Obesity

Less common

- Cushing's syndrome
- Acromegaly
- Malignancy
- PCOS
- Other states of hyperinsulinaemia

GENERAL MECHANISM/S

The mechanism is complex, with the key factor in most cases being insulin *resistance*. This leads to *hyperinsulinaemia* which in turn stimulates the *proliferation of keratinocytes (which contain melanin) and fibroblasts*.

Detailed mechanism/s

Keratinocytes normally multiply to form a thickened keratin (a fibrous structural protein) layer of the skin. In doing so, they take up the dark pigment *melanin* and deposit it in their nuclei. Excess proliferation of these cells, stimulated by hyperinsulinaemia, leads to a thicker-than-normal layer as well as a darker pigment because more melanin is present.

Similarly, fibroblasts produce collagen. Excess proliferation leads to additional collagen deposition and, when combined with the additional keratin layer, may contribute to the distinctive feel of AN.

Hyperinsulinaemia stimulates proliferation by:

1. directly stimulating insulin-like growth factor-1 (IGF-1) receptors on fibroblasts and keratinocytes causing proliferation
2. decreasing levels of some IGF-1-binding proteins. This allows for an increased level of free IGF-1 in circulation, which stimulates the IGF-1 receptor on fibroblasts and keratinocytes leading to proliferation.[1]

Other mediators may include:

- epidermal growth factor receptor (EGFR)
- fibroblast growth factor receptor (FGFR)
- androgens.

Three types of insulin resistance have been described:[2]

- type A – dysfunction of insulin receptors
- type B – caused by antibodies against insulin receptors
- type C – post-insulin receptor defects.

Any of these defects may cause hyperinsulinaemia and, thus, acanthosis nigricans.

There is evidence that in obesity there is dysfunction of the insulin receptors, leading to a compensatory rise in insulin levels. The high levels of insulin may then stimulate IGF-1 receptors on keratinocytes, stimulating proliferation.

In acromegaly two pathways contribute to AN. Firstly, the excess of growth hormone causes increased production of IGF-1, which stimulates the IGF-1 receptor on keratinocytes. Secondly, in acromegaly insulin resistance occurs, leading to hyperinsulinaemia and insulin-based stimulation of keratinocytes and fibroblasts.[3]

Some malignancies can cause AN, such as those that produce insulin receptor antibodies (stimulating

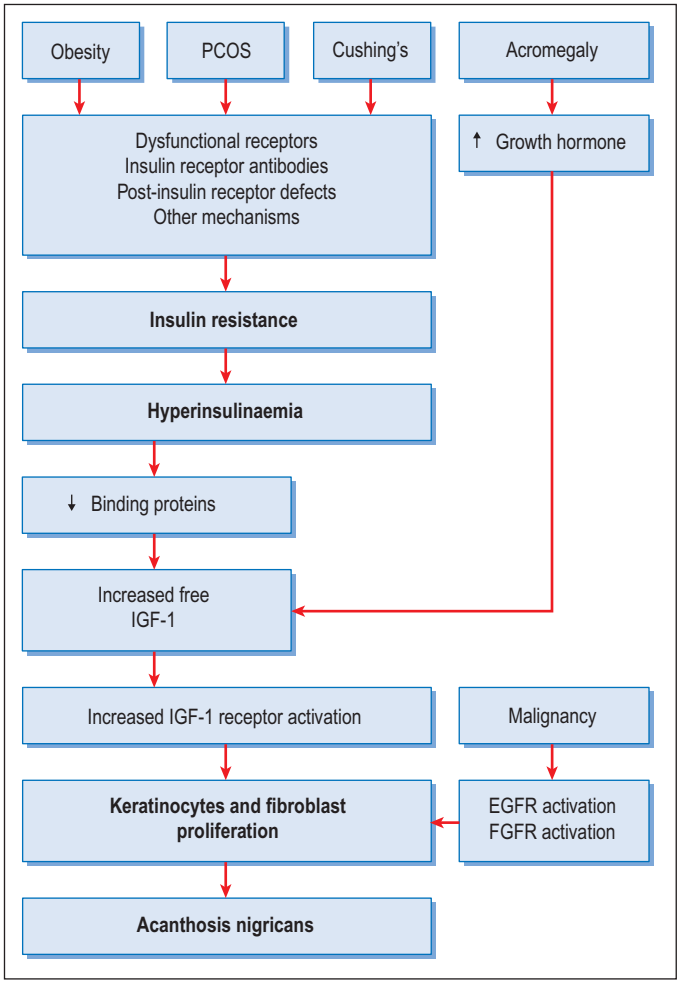

FIGURE 7.2 Mechanisms of acanthosis nigricans

secretion of insulin) or that produce other growth factors like epidermal growth factor,[4] which can also contribute to this sign.

SIGN VALUE

The exact prevalence is unclear and varies greatly with different population groups. AN has been shown to be a valuable indicator of hyperinsulinism and insulin resistance in adults and children.[5–7] Further, AN has been strongly associated with multiple risk factors for type 2 diabetes[8–10] and the development of metabolic syndrome,[5] and is correlated strongly with the level of obesity. It has also been suggested that it is an independent risk factor for the development of diabetes.[11] Research is still ongoing as to the utility of AN as a prognostic indicator in children. Recent research has shown that, in patients as young as 8–12 years with AN, more than 25% already had altered glucose metabolism.[5]

Angioid streaks

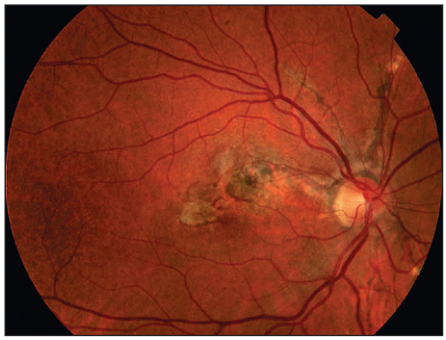

FIGURE 7.3 Angioid streaks

Reproduced, with permission, from Kanski JJ, *Clinical Diagnosis in Ophthalmology*, 1st edn, Philadelphia: Mosby, 2006: Fig 13-78.

DESCRIPTION

Angioid streaks appear as irregular, jagged, tapering lines that radiate from the peri-papillary retina into the macula and peripheral fundus.[12]

CONDITION/S ASSOCIATED WITH

More common

- Pseudoxanthoma elasticum
- Paget's disease of bone
- Haemoglobinopathies

Less common

- Ehlers–Danlos syndrome
- Acromegaly
- Neurofibromatosis

MECHANISM/S

Angioid streaks are thought to result from *small breaks within a brittle or calcified Bruch's membrane*. The specific mechanism for the abnormality in Bruch's membrane has not been established. Suggested factors include:

- elastic degeneration of the membrane
- iron deposition in elastic fibres from haemolysis with secondary mineralisation[13]
- nutritional impairment due to sickling, stasis and small vessel occlusion.

It is thought that lines of force from intra- and extraocular eye muscles cause the brittle membrane to crack.

SIGN VALUE

Nearly 50% of patients with angioid streaks have an underlying disease so, if present, investigation is warranted. Some studies have shown:

- 80–87% of patients with pseudoxanthoma elasticum had angioid streaks.[13]
- 2–15% of patients with Paget's disease had angioid streaks.[13]
- 0–6% of patients with haemoglobinopathy will develop them.[14]
- It is not a valuable sign for acromegaly.

Atrophic testicles

DESCRIPTION

Testicles of smaller than normal size. The mean volume of the adult testis is said to be 18.6 ± 4.8 mL.[2] Testicles are often measured by using an ellipsoid orchidometer – by this method most adult males have a volume >15 mL per testicle.[2]

CONDITION/S ASSOCIATED WITH

More common

- Trauma
- Cirrhosis of the liver
- Varicocoele

Less common

- Klinefelter's syndrome
- Prader–Willi syndrome
- Hypopituitarism
- Infection
- Anabolic steroid use

MECHANISM/S

70–80% of testicular volume is made up of seminiferous tubules, so any damage or dysfunction relating to these may cause atrophy.

Normal development of the testicles requires adequate blood flow and appropriate amounts of luteinising and follicular hormones. Testicular atrophy can be caused by *ischaemia, trauma,* lack of *hormonal* stimulation *(as primary or secondary hypogonadism)* or a primary *genetic* abnormality.

Klinefelter's syndrome (47XXY)

In Klinefelter's syndrome, a genetic abnormality results in an extra X chromosome. As part of this syndrome, as gonadotropins (LH and FSH) rise during puberty, the seminiferous tubules fibrose and shrink and may become obliterated. Hence, the volume of the testicle is reduced. Why this occurs is unclear.

Prader–Willi syndrome

A genetic abnormality on chromosome 15 leads to decreased production of GnRH, which causes low or altered FSH/LH levels and less stimulus for the testicles to produce testosterone and sperm. As a result of 'under-utilisation', the testicles atrophy.

Anabolic steroid use

Exogenous steroids cause suppression of the hypothalamic axis, in particular LH production, and therefore suppression of testosterone production, ultimately leading to atrophy.

Varicocoele

Varicocoeles cause testicular dysfunction and in some cases atrophy through a number of factors, including increased scrotal temperature, altered blood flow, increased oxidative stress and decreased testosterone production.

Cirrhosis of the liver

The damaged liver is unable to break down androgens, which means that there is more androgen available for peripheral conversion to oestrogen. The liver is also unable to break down normally produced available oestrogens. High levels of oestrogen cause reduced testosterone and sperm production and decreased seminiferous tubule size, resulting in testicular atrophy.

Alcohol

Alcohol causes atrophy of the testicle through direct and indirect mechanisms.

- Direct: alcohol and some of its breakdown products are toxic to Lleydig cells and decrease spermatogenesis.
- Indirect: alcohol can suppress hypothalamic and pituitary function. Studies have shown reduced LH levels with alcohol use.[15,16]

SIGN VALUE

Although it is a non-specific sign, if testicular atrophy is present, investigations for other underlying hormonal symptoms, signs and causes should be carried out.

Ballotable kidney

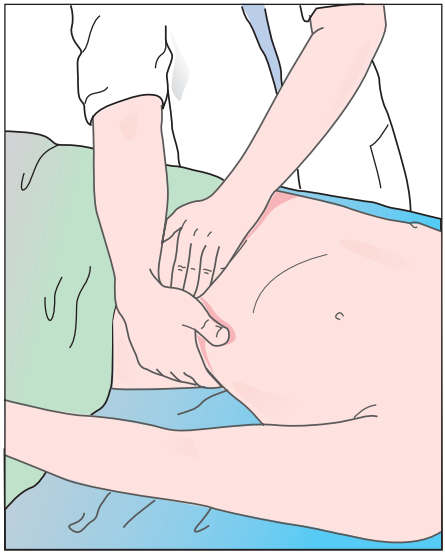

FIGURE 7.4 Balloting the kidneys

DESCRIPTION

With the patient supine, one hand is placed over the flank, and the other on the anterior aspect of the costophrenic angle. The hand underneath 'ballots' (from the French 'to toss') the kidney upwards. The kidney is ballotable if felt by the anterior hand during this manoeuvre.

CONDITION/S ASSOCIATED WITH

More common

- Polycystic kidney disease

Less common

- Renal cell carcinoma
- Wilm's tumour
- Amyloidosis
- Lymphoma
- Ureteric obstruction – hydronephrosis

MECHANISM/S

An enlarged kidney, from whatever cause (e.g. tumour/amyloid infiltration or aberrant cystic expansion), is closer in proximity to the anterior abdominal wall and is more likely to come into contact with the wall and thus be felt when pushed upwards.

SIGN VALUE

There is little or no evidence on the value of the ballotable kidney. In general, they are unlikely to be palpable, so if they are felt investigation is needed. However, a non-ballotable kidney by no means excludes pathology in the kidneys.

Bruising

DESCRIPTION

This refers to bruising caused by minimal trauma (i.e., an insult that would not normally result in a bruise).

CONDITION/S ASSOCIATED WITH

- Cushing's syndrome
- Uraemia

See 'Ecchymoses, purpura and petechiae' in Chapter 4, 'Haematological/oncological signs', for further causes.

MECHANISM/S

Cushing's syndrome

Loss of subcutaneous connective tissue due to the catabolic effects of glucocorticoids exposes underlying vessels that can easily rupture. It is a similar mechanism to that of striae.

Uraemia

The mechanism is complex and unclear.

It is thought that uraemic blood alters *platelet function, causing ineffective activation, aggregation and attachment* to blood vessel endothelium[17] rather than thrombocytopenia.

Key factors involved in this clotting dysfunction are shown in Figure 7.5.

- *Platelet function.* Defects in secretion of pro-aggregation factors, an imbalance between platelet agonists and inhibitors, excess parathyroid hormone that inhibits platelet aggregation and decreased thromboxane A2 all contribute to either ineffective activation or aggregation.[17]
- *Vessel wall attachment.* Several factors contribute to inefficient vessel wall attachment. Normally, platelets have certain proteins that are responsible for attachment to both other platelets and vessel endothelium – helping clot formation and stopping bleeding. 'Uraemic' toxins cause drops in glycoprotein[18,19] GP 1b and dysfunction in other receptors (α_{IIb} β_3) that are needed for attachment to blood vessel walls and normal interaction with vWF

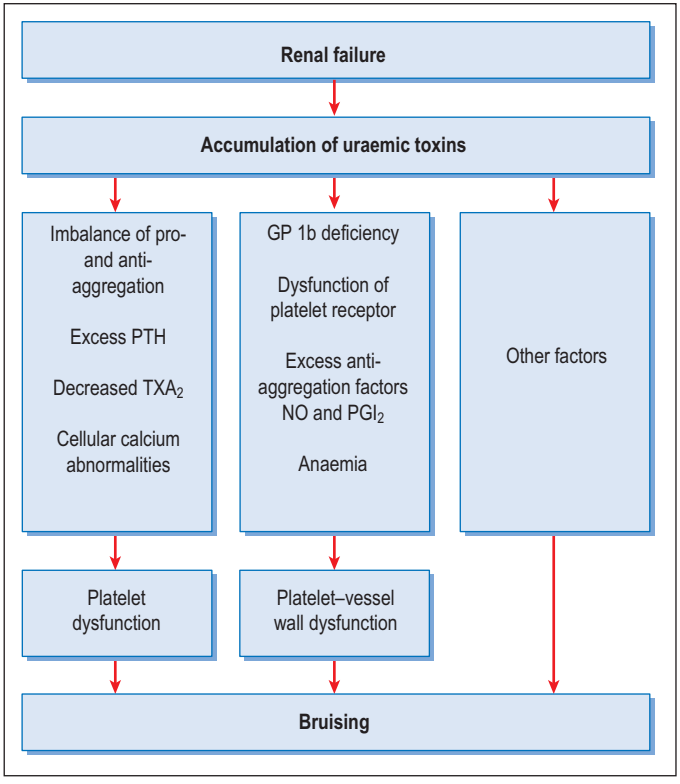

FIGURE 7.5 Mechanism of bruising in renal failure

and fibrinogen, thus inhibiting effective platelet clotting. In addition, increases in other elements that inhibit platelet clotting, such as NO and PGI_2, are also seen in uraemic patients. These increased inhibitors may also contribute to defective platelet clotting and thus easy bruising.[17]

- *Anaemia.* Red blood cells are integral to the normal platelet activation and clotting process. In normal quantities, they 'push' platelets towards the vascular endothelium and increase ADP-enhancing platelet activation. Uraemic patients are often anaemic and these normal processes are often diminished or absent, contributing to prolonged bleeding time. Some studies have suggested that this is the primary reason for prolonged bleeding time in uraemic patients.[20]
- *Other factors.* Drugs, including cephalosporins and aspirin, have been shown to affect platelet function.

Chvostek's sign

See also 'Trousseau's sign' in this chapter.

DESCRIPTION

Tapping on the patient's cheek at a point anterior to the ear and just below the zygomatic bone to stimulate the facial nerve and result in twitching of the ipsilateral facial muscles. It is suggestive of latent tetany and increased neuromuscular excitability.

CONDITION/S ASSOCIATED WITH

More common

Hypocalcaemia of any cause:

- Hypoparathyroidism
- Low vitamin D
- Pseudohypoparathyroidism
- Pancreatitis
- Hyperventilation/respiratory alkalosis

Less common

- Hypomagnesaemia

MECHANISM/S

All of the conditions associated with Chvostek's sign cause *increased neuronal excitability*. This increased excitability means that, when the facial nerve is stimulated (e.g. by tapping it with a finger), it is *more* likely to fire and stimulate muscle contraction.

Hypocalcaemia

Calcium is needed to maintain normal neuronal membrane permeability; it is thought to do this by acting on and blocking *sodium channels* on the neuronal membrane.[21] When extracellular calcium is low and/or not available to block them, the *sodium channels are more permeable*. More sodium enters the cell; the cell becomes less polarised and is more easily stimulated to reach action potential.

Respiratory alkalosis/hyperventilation

Respiratory alkalosis and hyperventilation result in a reduction in active *ionised calcium* – as opposed to total calcium. It is the decrease in *ionised calcium* that causes increased excitability.

Respiratory alkalosis most often occurs due to hyperventilation. When a patient hyperventilates, s/he blows off carbon dioxide. The alteration in CO_2 shifts the Henderson–Hasselbach equation in favour of CO_2 production in order to replace losses.

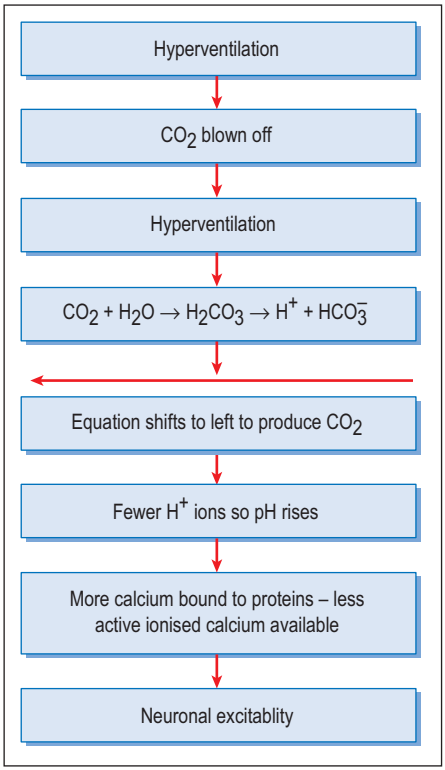

FIGURE 7.6 Mechanisms of Chvostek's sign in hyperventilation

The end result of this is a drop in circulating H^+ ions and, therefore, alkalosis. The amount of calcium that is free and ionised (or unbound to proteins) is heavily dependent on serum pH. When the pH is high (alkalotic), more calcium binds to proteins making less active calcium available in the extracellular fluid for normal activities, such as blocking sodium channels and maintaining membrane stability.

Hypomagnesaemia

How hypomagnesaemia causes tetany is not completely understood. However, it is clear that magnesium is essential *for maintaining ion channels and transporters in excitable tissues*.

Magnesium influences a number of cellular processes including:

- Na^+/ATPase activity – low magnesium decreases Na^+/ATPase activity
- blocking potassium channels on cells – low magnesium allows greater loss of potassium from cells
- low magnesium inhibits parathyroid hormone and can lead to hypocalcaemia – which can contribute to tetany
- calcium ion channel activity.

SIGN VALUE

There is little evidence for the value of examining for a positive Chvostek's sign. Nonetheless, it is accepted as a crude test for hypocalcaemia and neuronal excitability. It is suggested that the specificity of the test is low as up to 25% of patients with normal calcium levels may exhibit the sign.[2]

Cushing body habitus

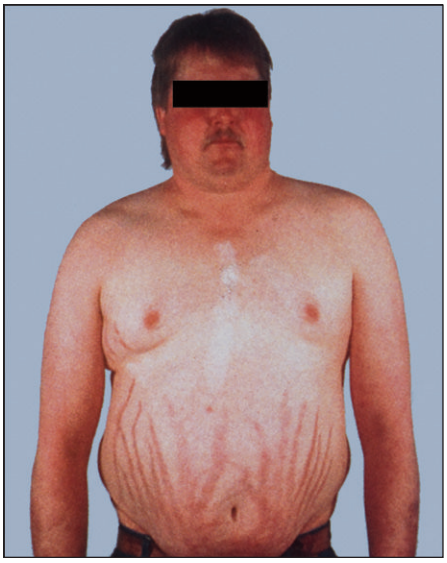

FIGURE 7.7 Central adiposity, moon facies; striae are also present

Reproduced, with permission, from Kumar V, Abbas AK, Fausto N, Aster JC, *Robbins and Cotran Pathologic Basis of Disease, Professional Edition*, 8th edn, Philadelphia: Saunders, 2009: Fig 24-43.

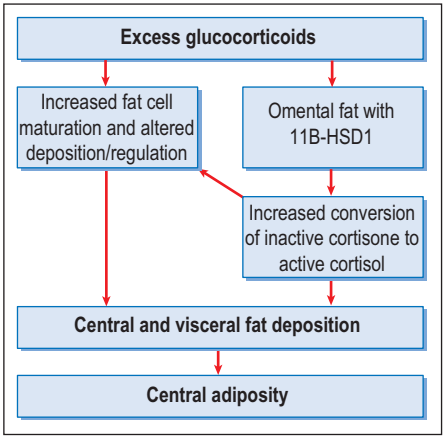

FIGURE 7.8 Mechanism of central adiposity in Cushing's syndrome

DESCRIPTION

Central adiposity

Progressive central obesity commonly involving the face, neck, chest and abdomen. Internal structures and organs are also affected.

Moon facies

An erythematous, rounded facial appearance as a result of fat deposition in the bitemporal regions.

Buffalo hump

Fat deposition between the scapulae and behind the neck.

Supraclavicular fat pads also indicate central adiposity.

CONDITION/S ASSOCIATED WITH

- Cushing's syndrome

CENTRAL ADIPOSITY MECHANISM/S

Central adiposity represents deposition of intra-abdominal visceral fat, NOT subcutaneous fat.

Glucocorticoids have been shown to regulate adipose tissue differentiation, function and distribution. They are potent activators of adipose stromal cells to become mature adipocytes or fat cells.

Studies have shown that certain types of fat, including omental (but **not** subcutaneous), are able to convert inactive cortisone to cortisol via an enzyme, 11B-HSD1.[21] Exposure to insulin and cortisol further increases the levels of this enzyme, causing even more production of active cortisol.

As a consequence, it is thought that chronic exposure to glucocorticoids can increase omental adipocyte generation of cortisol, which stimulates more adipocytes into differentiating into mature fat cells, causing central adiposity.[22]

The cause of preferential deposition in the face (moon facies) and posterior neck (buffalo hump) is not clear.

SIGN VALUE

- Central obesity is said to be the most common initial sign, present in over 90% of patients according to some texts.[6]
- Other texts suggest frequency between 44% and 93%[23] with a LR of 3.0 if present.
- Moon facies is seen in 67–100% of patients,[2] with sensitivity of 98% and specificity of 41% for Cushing's syndrome.[24]
- A buffalo hump may also be seen in other conditions, including AIDS and generalised obesity, and is not specific for Cushing's syndrome.

Diabetic amyotrophy (lumbar plexopathy)

DESCRIPTION

Diabetic neuropathy associated with painful muscle wasting, particularly affecting the thighs, legs and buttocks, with reduced reflexes and power in the lower limbs. Marked weight loss is common.

It typically resolves after 12 or more months.

CONDITION/S ASSOCIATED WITH

- Diabetes

MECHANISM/S

The mechanism is unclear; possibly a form of lumbosacral plexopathy.

Previously, ischaemic injury, metabolic derangement and inflammation have been suggested as causes.[25]

Studies have shown inflammatory infiltrates, immunoglobulin and complement depositions in the small blood vessels,[26–29] suggesting an *immune-mediated vasculitis* may be the cause.

Diabetic retinopathy

DESCRIPTION

Diabetic retinopathy is an umbrella term used to describe a number of characteristic changes seen in the eye in the setting of diabetes. Some of the terms and causes overlap with hypertensive retinopathy and have common final pathways. See 'Hypertensive retinopathy' in Chapter 3, 'Cardiovascular signs'. Broadly speaking, diabetic retinopathy can be broken down into the categories shown in Table 7.1.

CONDITION/S ASSOCIATED WITH

- Diabetes
- Hypertensive retinopathy can also display similar changes

MECHANISM/S

The mechanism behind the changes seen in diabetic retinopathy is very complex and as yet has not been fully explained.

Chronic hyperglycaemia is thought to be the main factor leading to diabetic retinopathy,[30] by commencing a series of changes that ultimately lead to two key pathological states:

1. *altered vascular permeability* – disrupted or leaky vessels
2. *ischaemia of the retina* with associated *neovascularisation*.

These changes are implicated in the vision-threatening forms of macular oedema and proliferative diabetic retinopathy.

Of course, there are many additional pathological processes that also contribute to the development of these two states. Table 7.2 contains some of the key components.

SIGN VALUE

Diabetic retinopathy is an important sign and must be monitored. The greater the extent of retinopathy at diagnosis, the higher the risk of progression; this reinforces the importance of tight blood glucose control in a person with the condition.[32] As proliferative retinopathy and macular oedema can be treated with success in most cases to prevent blindness, both screening for and detecting the clinical sign in any setting is essential.

Changes associated with diabetic retinopathy are seen in:

- almost all patients who have had type 1 diabetes for 20 years
- 80% of patients who have had type 2 diabetes for 20 years.

After 10 years, proliferative retinopathy is seen in 50% of patients with type 1 diabetes[33] and 10% of patients with type 2 diabetes.[32]

TABLE 7.1 Diabetic retinopathy changes

Nonproliferative retinopathy	
Cotton wool spots	Ischaemic swelling of the optic nerve layer causes a white, round or patchy appearance
Dot and blot haemorrhages	Larger red dots with distinct (dot) or indistinct (blot) borders
Hard exudates	Lipids deposited within the retina create white or yellowish deposits with a waxy appearance
Microaneurysms	Distinct round red dots
Proliferative retinopathy	
Neovascularisation arising from the optic disc or vessels	
Macular oedema	
Thickening and oedema involving the macula (may occur at any stage of proliferative or non-proliferative diabetic retinopathy)	

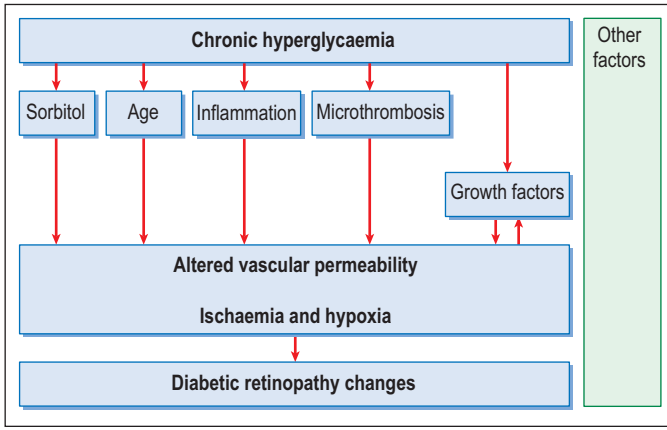

FIGURE 7.9 Simplified mechanism of diabetic retinopathy

TABLE 7.2 Mechanism/s and effects that contribute to diabetic retinopathy

Proposed mechanism	Effect
CHRONIC HYPERGLYCAEMIA	Hyperglycaemia impairs retinal blood flow autoregulation[31] – causing increased flow, leading to shear stress on retinal blood vessels. This leads to the release of vasoactive substances, which results in vascular leakage and *macular oedema.* Contributes to sorbitol production – see below
SORBITOL	Sorbitol is formed in the breakdown of glucose. Excess sorbitol can cause osmotic damage to cells and alter other proteins – leading to altered vascular permeability
ADVANCED GLYCATED END PRODUCTS	Excess glucose combines with amino acids and proteins, inactivates key enzymes and alters cellular proteins,[30] induces reactive oxygen species and contributes to inflammation. The result of this is vascular damage and ischaemia. Glucose may also link with collagen and initiate microvascular complications
VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)	VEGF is induced by retinal hypoxia[30] and can cause blood–retina barrier breakdown, leading to macular oedema. VEGF is also key in inducing the new blood vessels seen in proliferative retinopathy
INFLAMMATION	Increased adhesion of leukocytes to capillary walls decreases blood flow and increases hypoxia. May contribute to breakdown of blood–retina barrier and development of macular oedema[30]
MICROTHROMBOSIS	Leads to occlusion of retinal capillaries, ischaemia and capillary leakage. Leakage, in turn, stimulates various growth factors including VEGF
OTHER FACTORS	Pigment – epithelial-derived factors
	Growth factors and IGF-1
	Reactive oxidative species

Based on Frank RN, N Engl J Med 2004; 350: 48–58; with permission.

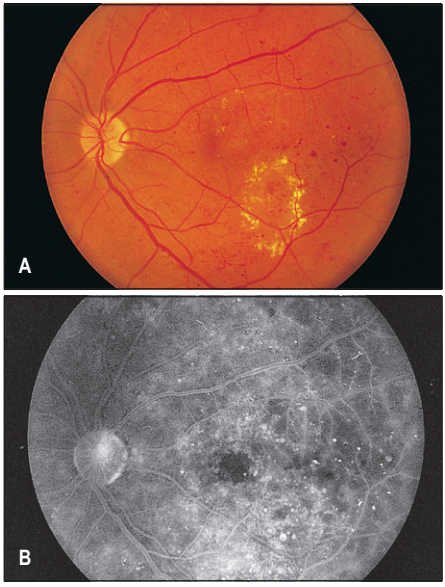

FIGURE 7.10 Nonproliferative diabetic retinopathy with microaneurysms

A Small dot haemorrhages, microaneurysms, hard (lipid) exudates, circinate retinopathy, an intraretinal microvascular abnormality and macular oedema. **B** Fluorescein angiography of the eye shown in **A**. Microaneurysms are seen as multiple dots of hyperfluorescence, but the dot haemorrhages do not fluoresce. The foveal avascular zone is minimally enlarged.

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, London: Mosby, 2008: Fig 6-19-1.

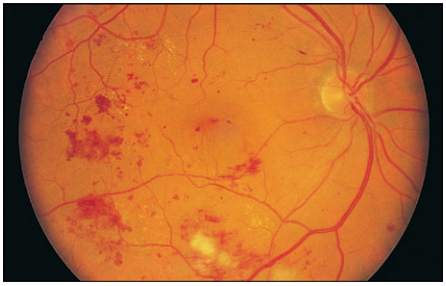

FIGURE 7.11 Nonproliferative retinopathy with some blot haemorrhages, splinter haemorrhages and cotton wool spots

Reproduced, with permission, from Yanoff M, Duker JS, *Ophthalmology*, 3rd edn, London: Mosby, 2008: Fig 6-19-2.

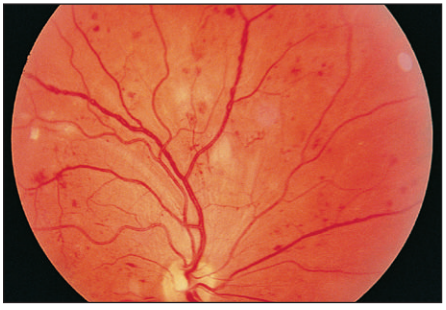

FIGURE 7.12 Severe proliferative diabetic retinopathy with cotton wool spots, intraretinal microvascular abnormalities and venous bleeding

Reproduced, with permission, from Goldman L, Ausiello D, *Cecil Medicine*, 23rd edn, Philadelphia: Saunders, 2007: Fig 449-16.

The ability of clinicians to diagnose *sight-threatening* retinopathy has also been assessed.[23] Key findings were:

- Macular oedema is rarely ever identified by non-specialists.
- Use of an ophthalmoscope by non-specialists with the patient's pupils dilated yielded sensitivity of 53–69% and specificity of 91–96% with a PLR of 10.2.

These findings suggest that the signs themselves are difficult for the non-specialist to sensitively detect!

Frontal bossing

DESCRIPTION

An unusual prominence of the forehead.

CONDITION/S ASSOCIATED WITH

More common

- Acromegaly – commonly associated but acromegaly itself is a rare hormonal condition
- Fragile X syndrome – a common cause of mental retardation in males, associated with a large cranium including prominent forehead
- Extramedullary haematopoiesis – see the description under 'Chipmunk facies' in Chapter 4, 'Haematological/ oncological signs'

Less common

- Basal cell naevus syndrome
- Congenital syphilis
- Cleidocranial dysostosis
- Crouzon syndrome
- Hurler syndrome
- Pfeiffer syndrome
- Rubinstein–Taybi syndrome
- Russell–Silver syndrome

MECHANISM/S

In acromegaly, too much circulating growth hormone causes excess growth of the cranium and, in particular, the bones of the forehead.

Galactorrhoea

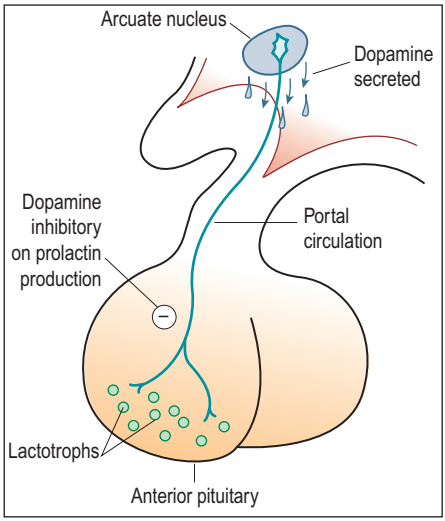

FIGURE 7.13 Dopamine–prolactin inhibition

DESCRIPTION

Lactation that occurs in the absence of breastfeeding in females. It is always pathological in males.

CONDITION/S ASSOCIATED WITH

- Hyperprolactinaemia (see Table 7.3)
- Idiopathic
  - Liver disease – rare
  - Hypogonadism

GENERAL MECHANISM/S

Prolactin normally stimulates breast and milk gland development as well as (with oxytocin) stimulating lactation in the post-partum period. Oestrogen and progesterone are also needed for breast development.

Normally, prolactin (unlike other pituitary hormones) is tonically **inhibited** by dopamine, which is persistently secreted by the arcuate nucleus and travels down

TABLE 7.3 Causes of hyperprolactinaemia

Physiological	Pharmacological	Pathological
	MORE COMMON	
Exercise	Dopamine antagonists • atypical and typical antipsychotics • metaclopramide	Prolactin-secreting adenoma
Pregnancy	H_2 antagonists (e.g. cimetidine)	Pituitary stalk compression
Puerperium	Methyldopa	Chest wall stimulation
Sleep	Oestrogens	Hypothyroidism
Nipple stimulation	Phenothiazines	
	LESS COMMON	
Seizures	Opiates	Acromegaly
Newborns	SSRIs	Hypoglycaemia
	Verapamil	Renal failure
	Tricyclic antidepressants	Multiple sclerosis
	MAOIs	Spinal cord lesions
	Oral contraceptive pill	

the pituitary stalk (on the tuberoinfundibular axis) and stops cells in the anterior pituitary (lactotrophs) from producing prolactin (see Figure 7.13).

Therefore, hyperprolactinaemia and galactorrhoea may be caused by:

1. excess prolactin secretion
2. disruption of the normal inhibitory process of dopamine
3. failed excretion of prolactin.

Note: Having hyperprolactinaemia does not necessarily mean galactorrhoea will follow.

Selected drug mechanism/s

The predominant effect of commonly used antipsychotics (e.g. olanzapine, risperidone) and anti-nausea medications (metaclopramide) is due to blocking of dopamine. This may cause the inhibitory of effect of dopamine on prolactin to be reduced, thereby producing hyperprolactinaemia.

Methyldopa depletes dopamine stores and competitively inhibits L-dopa conversion to dopamine, thereby reducing dopamine and therefore inhibition of prolactin.

Verapamil has a side effect of directly stimulating lactotrophs,[34] thus producing more prolactin.

SSRIs increase the level of serotonin available, which has a stimulating effect on prolactin secretion.

Prolactinomas

Prolactinomas are a type of pituitary adenoma, which is a neoplastic growth of pituitary lactotroph tissue. Prolactinomas secrete prolactin in large quantities and are not effectively inhibited by normal levels of dopamine.

Pituitary stalk compression

Stalk compression by any cause (e.g. craniopharyngioma, trauma, pituitary adenoma) disrupts or destroys the normal tuberoinfundibular pathway that allows dopamine to travel from the arcuate nucleus, via the portal circulation, to the lactotrophs to inhibit prolactin secretion. Hyperprolactinaemia results.

Hypothyroidism

In hypothyroidism thyrotrophin-releasing hormone (TRH) is elevated in a compensatory response to low thyroxine. TRH is a potent prolactin-releasing factor.

Chest wall stimulation

Chest wall stimulation due to any cause (e.g. breast surgery, mechanical trauma, herpes zoster) can produce a neurogenic reflex to stimulate the production of prolactin[2] via the suppression of dopamine.

It is thought that stimuli are passed via the intercostal nerves to the posterior column of the spinal cord, to the brainstem and then the hypothalamus where dopamine secretion is reduced.[34]

Acromegaly

Hyperprolactinaemia and galactorrhoea may result from:

1. mass effect of the pituitary adenoma causing stalk compression
2. excess growth hormone that has a stimulatory effect on prolactin
3. in very rare cases, a pituitary adenoma may produce both growth hormone and prolactin.

Renal failure

Decreased clearance of prolactin is thought to be the mechanism.

Newborn galactorrhoea

High maternal oestrogen levels pass through the placenta, causing development of the foetal breast tissue.

SIGN VALUE

Galactorrhoea in any man, and in a non-breastfeeding woman, warrants some attention. It is a non-specific sign that, if present, requires a thorough history and examination in an attempt to find more localising signs. Some key facts to remember:

- Galactorrhoea will occur in a majority of women with prolactinomas but is much less common in males.[2]
- 13% of patients with acromegaly may display galactorrhoea[2] and 10% of patients with primary hypothyroidism will have high levels of prolactin.[35]
- Less than 10% of cases of galactorrhoea are caused by systemic diseases;[36] medication-induced, idiopathic, physiological and neoplastic (e.g. prolactinoma) causes are more common.

Goitre

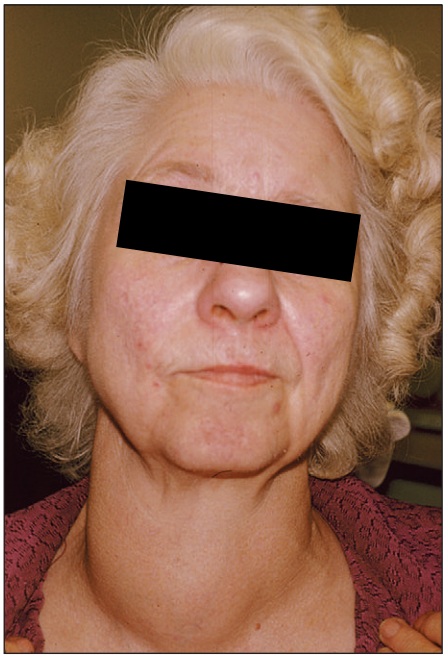

FIGURE 7.14 Large goitre

Reproduced, with permission, from Little JW, Falace DA, Miller CS, Rhodus NL, *Dental Management of the Medically Compromised Patient*, 7th edn, St Louis: Mosby, 2008: Fig 1-12.

DESCRIPTION

An enlargement of the thyroid gland causing a swelling in the front of the neck,[37] which is often both visible and palpable on examination.

CONDITION/S ASSOCIATED WITH

- Graves' disease
- Hashimoto's disease
- Congenital
- Adenomatous (thyroid adenoma)
- Iodine deficiency
- Toxic multinodular
- Thyroid carcinoma

MECHANISM/S

The mechanism of goitre development depends on the underlying cause. However, the final common pathway for most goitres will involve one or more of the following:

1. primary TSH stimulation (or TSHR stimulation by an antibody in Graves' disease) of thyroid cells causing cellular hyperplasia
2. TSH stimulation of thyroid cells causing cellular hyperplasia secondary to low levels of thyroid hormone through problems with thyroid hormone production or secretion
3. autonomous hyperfunction.

Table 7.4 summarises the various causes of goitres and the relevant mechanism/s

SIGN VALUE

Goitre (regardless of type) is found in 70–93%[41–43] of patients with hyperthyroidism. It therefore has relatively good sensitivity. However, up to 30% of elderly patients have been found to have goitre without underlying thyroid disease so it is less valuable as a specific sign[10] for hormonal disturbance. A goitre with a focal nodule in the thyroid should always be investigated to exclude thyroid cancer, especially in the setting of a euthyroid state.

TABLE 7.4 Mechanisms of goitre development

Hyperthyroid goitres	Mechanism
Graves' disease	*Thyroid receptor antibodies stimulate TSH receptors* on the thyroid gland, causing cellular hyperplasia and thyroid gland hypertrophy
	Infiltration of immune cells may also contribute to enlargement
Toxic multinodular goitre	*Autonomous hyperfunction*. Goitres can change from TSH-dependent hyperplasia to autonomous hyperfunction. Oxygen reactive species and other processes may precipitate gene mutations, leading to chronic activation of the Gs and/or other proteins, which causes chronic proliferation of thyroid cells[2,38]
Single toxic adenoma	*Autonomous hyperfunction* as described above
Iodine deficiency	In iodine deficiency, the cause of the goitre is *still TSH over-stimulation and cellular hyperplasia* but it is secondary to *impaired hormone synthesis*.
	An iodine level of less than 0.01 mg (10 μg) per day impedes thyroid hormone synthesis. In response to low levels of thyroid hormones, more TSH is produced and secreted via feedback mechanisms, causing cellular hyperplasia
Iodine excess	Excess iodine *can block the secretion of thyroid hormones, leading to low levels* and a compensatory rise in TSH, and therefore *TSH-related cellular hyperplasia*[39]
Congenital disorders	Defects in hormone synthesis result in a compensatory rise in TSH and, consequently, TSH-stimulated cellular hyperplasia
Adenomatous	Mutations in the TSH pathway, most often the TSH receptor and Gs unit, lead to excess cAMP and the production of a few 'highly growth-prone cells' that, when stimulated by TSH, grow exponentially more than the homogenous surrounding tissue, producing an adenoma[40]
Goitrogens (e.g. cabbage, turnips, lithium, sulfonylureas)	Block secretion of thyroid hormone[39]
Hypothyroid/ euthyroid goitres	
Hashimoto thyroiditis	*Secondary rises in TSH and lymphocytic invasion* are responsible for goitre formation in Hashimoto's disease.
	In Hashimoto thyroiditis, lymphocytes are sensitised to the thyroid gland and destroy normal architecture. This destruction in the gland causes a drop in T_3 and T_4, and a compensatory rise in TSH, which causes goitre development through cellular hyperplasia. Heavy lymphocytic infiltration also adds to the formation of the goitre

Granuloma annulare

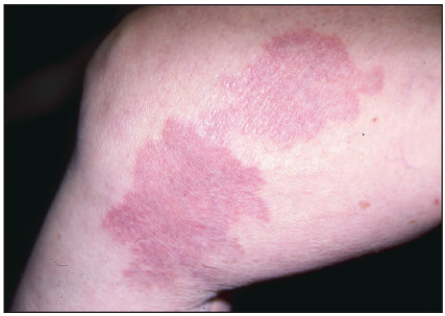

FIGURE 7.15 Granuloma annulare

Reproduced, with permission, from Rakel RE, *Textbook of Family Medicine*, 7th edn, Philadelphia: Saunders, 2007: Fig 44-27.

DESCRIPTION

Characterised by a ring of small, firm flesh-coloured or red papules, often found on the dorsal surfaces of hands and feet.[44] They may develop a rolled border with central clearing.

May be localised or disseminated across the body, subcutaneous or perforating (reaching deeper into subcutaneous tissue).

CONDITION/S ASSOCIATED WITH

More common

- Infections and immunisations (e.g. herpes zoster; hepatitis B, C)
- Trauma
- Diabetes mellitus (historically, type 1 DM)

Less common

- Drugs (e.g. gold therapy, allopurinol, amlodipine)
- Malignancy (e.g. Hodgkin's and non-Hodgkin's lymphoma, leukaemia)
- Rheumatoid arthritis

MECHANISM/S

The mechanism behind the development of connective tissue surrounded by inflammatory infiltrate is not clear.

Mechanisms suggested have included:[45]

1. primary degeneration of connective tissue initiating granulomatous inflammation
2. lymphocyte-mediated immune reaction leading to macrocyte and cytokine activation and destruction of connective tissue
3. a vasculitis or other microangiopathy causing tissue injury.

SIGN VALUE

Limited evidence exists on the true value of the sign.

Historically, granuloma annulare has been associated with type 1 diabetes and the degree to which it is related reviewed multiple times, without a definite link being found. Some of the evidence regarding this is as follows:

- Cases have been reported with type 2 DM.[46]
- It rarely pre-dates the development of diabetes.[46]
- In one study of 100 patients with granuloma annulare, 21% of patients with the generalised disease had diabetes.[47]
- However. another study found a higher incidence of diabetes in localised granuloma.[48]

Graves' ophthalmopathy (orbitopathy)

DESCRIPTION

Graves' ophthalmopathy encompasses a number of eye signs and changes frequently seen in Graves' disease. The progression in severity of these is classified in Table 7.5.

CONDITION/S ASSOCIATED WITH

- Graves' disease

MECHANISM/S

Much progress has been made towards identifying specific mechanisms in Graves' disease. Key to the development of many of the signs is *immunoreactivity against the thyrotropin receptor, including autoantibodies,* and the *dysregulation of normal orbital fibroblast function by this autoimmune immunoreactivity.*[49] Through a variety of processes explained below, this results in ocular muscle swelling and fibrosis.

In Graves' disease anti-thyroid receptor antibodies are produced as part of the disease process. These antibodies that act on the thyroid also affect orbital fibroblasts. When stimulated by thyroid autoantibodies and cytokines, fibroblasts proliferate and produce large amounts of *hydrophilic* hyaluronan, a type of glycoaminoglycan that *attracts and sequesters fluid.* At the same time, a *subgroup of fibroblasts differentiates into mature adipocytes.* It is these two changes (with associated lymphocytic infiltration) that result in the enlarged ocular muscles and orbital fat pads seen in patients with Graves' ophthalmopathy.

In addition to this, stimulation of *insulin-like growth factor receptor* on orbital fibroblasts results in the recruitment of more activated T cells and immune cells. This further stimulates existing fibroblasts to produce prostaglandin E2 and hyaluronan,[1] which accumulates between muscle fibres, making them bigger.

Activated immune cells also produce *proadipogenic substances* that stimulate the maturation of more adipocytes, which expands tissue volume even more.

With the increase in size of soft tissue and muscles involved with the orbit (due to the combination of adipocytes, hylauronan and inflammatory cell infiltrates), pressure within the orbital cavity is increased – ultimately affecting the function of the eye.

It should be noted that, in contrast to Graves' ophthalmopathy, the eye sign of lid lag is a feature of thyroid overactivity (hyperthyroidism) due to increased activity of the levator palpebrae superioris.

Summary of eye sign mechanism/s

There are a large number of eye signs associated with Graves' disease. Some descriptions are similar and almost overlap, and often the underlying mechanisms contribute to the development of multiple signs. Table 7.6 summarises a collection of signs that may be seen on physical exam.

TABLE 7.5 Classification of eye changes seen in Graves' disease

Class	Definition
0	No signs or symptoms
1	Only signs (e.g. lid lag, upper lid retraction, stare)
2	Soft tissue involvement: periorbital oedema, congestion/redness of the conjunctiva, chemosis
3	Proptosis
4	Extraocular involvement: upward gaze limitation, lateral gaze limitation
5	Corneal involvement: keratitis
6	Sight loss: optic nerve involvement

Based on Werner SC, J Clin Endocrinol Metab 1969; 29: 782 and 1977; 44: 203; with permission.

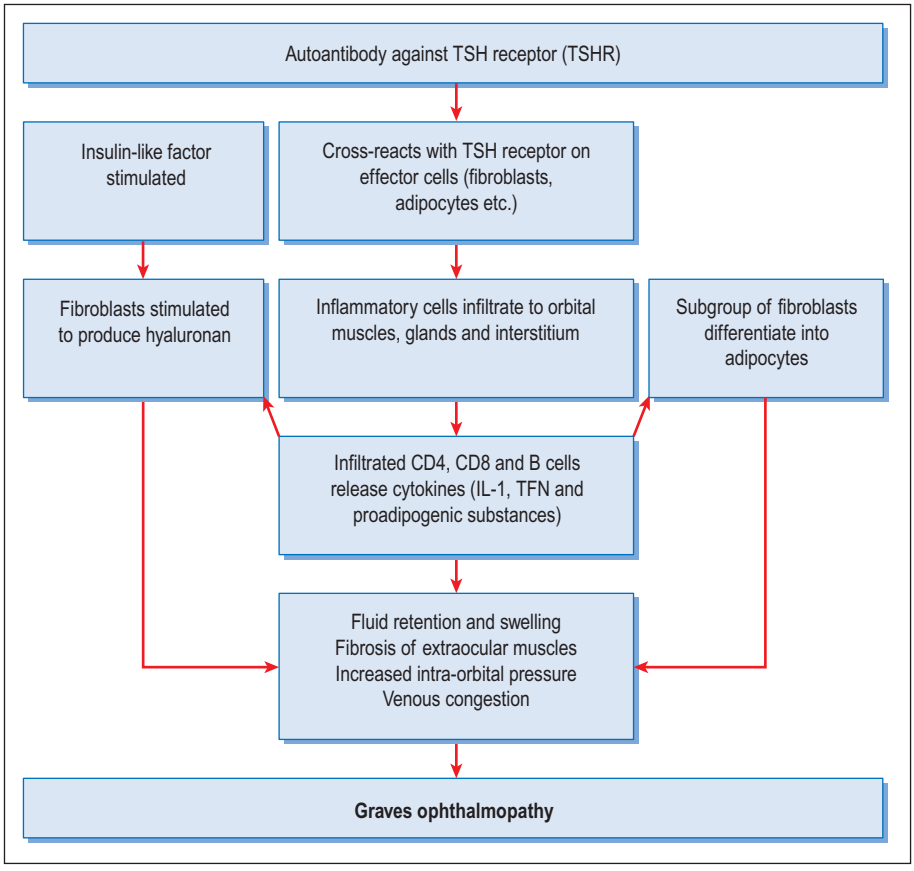

FIGURE 7.16 Simplified mechanism of Graves' ophthalmopathy

SIGN VALUE

Graves' orbitopathy or ophthalmopathy is common. Approximately 35–50% of patients with Graves' disease suffer from one or more features,[49,51] 3–5% of patients suffer from severe eye disease,[52] and up to 70% of patients have subclinical eye disease identified on imaging. Many of the signs are very specific for underlying Graves' disease. Quantifying the value of each individual sign is difficult; however, there is some evidence for the following:

- Lid retraction has a sensitivity of 34% and specificity of 99% and LR of 31.5 for Graves' disease.[41]
- Lid lag has a sensitivity of 19% and specificity of 99% and LR of 17.6 for Graves' disease.[41]

TABLE 7.6 Summary of eye signs in thyrotoxicosis and mechanism/s

Name	Description	Mechanism
Upper lid retraction	The upper eyelid is noticeably retracted, exposing an abnormal amount of the upper sclera. It may produce Dalrymple's sign (described below)	Contributing factors include:[49] • Excess thyroid hormone causes increased sympathetic stimulation of the superior tarsal muscle (aka Mueller's muscle – a sympathetically innervated smooth muscle that assists in elevating the eyelid) • Over-activation of the levator muscle as it contracts against a tight inferior rectus muscle • Scarring between levator and surrounding tissues does not allow for normal closure
Von Graefe's sign	A dynamic abnormality; as the eye moves down, the eyelid does not follow smoothly but at a slower rate, exposing the superior limbus[50]	The specific mechanism has not been elucidated. Likely a combination of factors contributing to upper lid retraction (see above)
Lagopthalmos	Inability to close the eyes	The specific mechanism is not known. Likely a combination of factors contributing to upper lid retraction (see above)
Abadie's sign	*Spasm* of the levator palpebrae when retracting the upper eyelid	The specific mechanism is not known. Likely a combination of factors contributing to upper lid retraction (see above)
Dalrymple's sign	*Widening of the palpebral fissure* Retraction of the *eyelids* on outward stare so that the palpebral opening is abnormally wide	A combination of: 1) proptosis, making it more difficult for the eyelid to cover all of the eye; and 2) hypertonicity/overactivation of the levator and Mueller's muscle, resulting in the upper lid retraction and hence widening of the palpebral fissure
Griffith's sign	Lower lid lag on upward gaze	Most likely over-activity/sympathetic stimulation of nerves supplying the lower eyelid, with or without mechanical restriction of muscles involved in eyelid closure
Stellwag's sign	Infrequent and incomplete blinking, often accompanied by Dalrymple's sign	Normal blinking is mainly controlled by the obicularis oculi (closing the eye) and levator palpebrae (opening the eye) with Mueller's muscle to assist in eye widening. Excess stimulation and over-activation of Mueller's muscle and levator palpebrae due to high levels of thyroid hormone causes the opening element of blinking to be accentuated

Diplopia	'Double vision'	Inflammation, swelling and eventually fibrosis of the extraocular muscles do not allow efficient conjugate eye movements, which normally maintain corresponding visual objects on the retinas of both eyes
Ballet's sign	Restriction of one or more extraocular muscles	Lymphocytic invasion, inflammation and oedema lead to fibrosis and scarring of the ocular muscles. Restriction of the range of movement then occurs
Chemosis	Swelling or oedema of the conjunctiva	Venous compression and decreased venous drainage are likely to contribute. Inflammatory cell infiltrate may also play a role
		Chemosis is also seen in reactions to allergies and foreign bodies
Gaze limitation	The normal range or field of vision is decreased	Inflammation, swelling and eventually fibrosis restrict the range of movement and contraction of the extraocular muscles. The eyeball cannot move as much and, therefore, vision becomes limited
Sight loss	Decreased vision	Progressive swelling of surrounding tissues raises the orbital bony cavity pressure to a point at which the optic nerve is compressed and/or damaged and vision is impaired or lost
Periorbital fullness	Swelling around the orbit	Primarily due to decreased venous drainage because of venous compression in the orbital space, leading to swelling of veins and capillaries and oedema[49]
Proptosis (exophthalmos)	Forward displacement of the eyes	Swelling of the ocular muscles, fat pads and tissues within the bony cavity 'pushes' the eyeball forward
Riesman's sign	Bruit heard over the closed eye with a stethoscope	Increased blood flow through the orbit caused by hyperdynamic state

Graves' orbitopathy

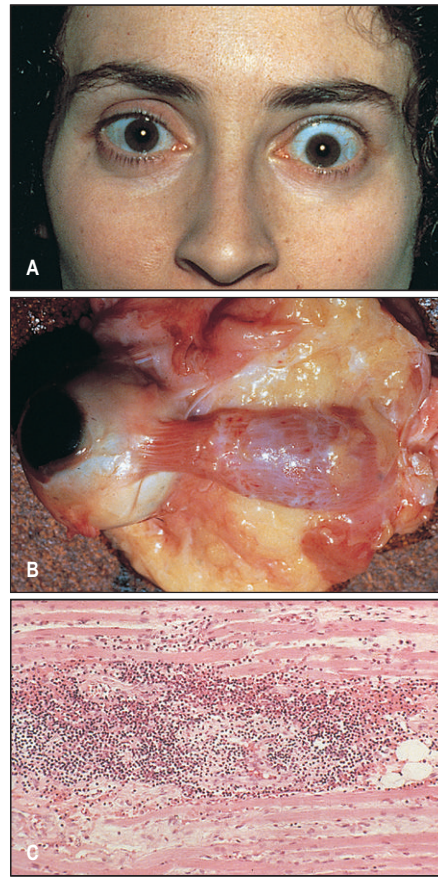

FIGURE 7.17 Graves' disease

A In Graves' disease, exophthalmos often looks more pronounced than it actually is because of the extreme lid retraction that may occur. This patient, for instance, had minimal proptosis of the left eye but marked lid retraction. **B** The orbital contents obtained post mortem from a patient with Graves' disease. Note the enormously thickened extraocular muscle. **C** Both fluid and inflammatory cells separating the muscle bundle may be seen. The inflammatory cells are predominantly lymphocytes, plus plasma cells.

Reproduced, with permission, from Yanoff M, Duker JS, *Opthalmology*, 3rd edn, London: Mosby, 2008: Fig 12-12-15.

Hirsutism

DESCRIPTION

Abnormal excessive hairiness, in particular associated with a male-type pattern of hair growth in women.

CONDITION/S ASSOCIATED WITH

More common

- Polycystic ovary syndrome (PCOS) – most common cause
- Cushing's disease
- Idiopathic

Less common

- Congenital adrenal hyperplasia
- Ovarian tumours
- Adrenal tumours
- Hyperthecosis – very rare

MECHANISM/S

While there are a number of causes, the common pathway of most mechanisms resulting in hirsutism is androgen excess. Androgens increase hair follicle size and hair fibre diameter and lengthen the growth phase. The most common androgens are testosterone, DHEA-S and androstenedione.

Polycystic ovary syndrome

PCOS results in *excess androgen production*. How it does this is still under investigation as is the pathogenesis of the syndrome itself. In normal ovaries, luteinising hormone (LH) stimulates theca cells to produce androgen precursors and androgens by means of a number of enzymes. In patients with PCOS, theca cells are simply more efficient at producing androgens.[53,54] The excess androgens, in turn, increase hair follicle size and diameter and lengthen the growth phase.

Factors contributing to the increased production of androgens in PCOS include:

- increased frequency of GnRH pulses and, therefore, LH pulses
- insulin (increased in PCOS) acts synergistically with LH to increase androgen production
- insulin also inhibits sex-binding hormone globulin, which binds to testosterone, thus increasing free or active testosterone.

Cushing's syndrome

The mechanism is not clear. Excess ACTH has been shown to cause hyperstimulation of the zona fasciculata and zona glomerulosa, producing cortisol and androgens.[2]

Congenital adrenal hyperplasia

In the most common form of congenital adrenal hyperplasia, there is a deficiency of the enzyme 21-hydroxylase. This enzyme is essential in the pathway that produces aldosterone and mineralocorticoids from cholesterol. When it is lacking, the pathway is shunted away from the production of mineralocorticoids to the production of androgens. The androgens then act on hair follicles to produce hirsutism.

Adrenal tumours

A rare cause of androgen excess.

Some tumours may secrete testosterone but most secrete DHEA and DHEA-S and cortisol, which then act on hair follicles as discussed above. In such cases, patients may be virilised and may have severe hirsutism in terms of the body sites (e.g. chest and back) and area affected.

SIGN VALUE

Seen in 60–70% of Cushing's syndrome.[2] Not specific to pathology, and most cases of hirsutism are idiopathic and benign.

Hypercarotinaemia/carotenoderma

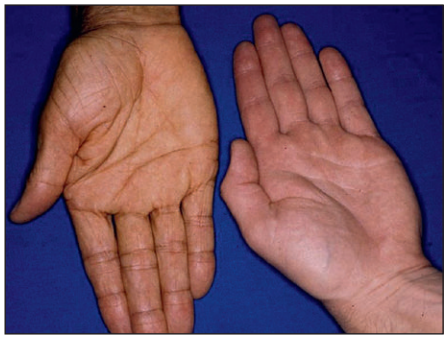

FIGURE 7.18 Carotenoderma (left) and normal hand (right)

Reproduced, with permission, from Haught JM, Patel S, English JC, J Am Acad Dermatol 2007; 57(6): 1051–1058.

DESCRIPTION

A yellow/orange discolouration of the skin that, unlike jaundice, often does not affect the sclerae. Often found over nasolabial folds, palms and soles.

CONDITION/S ASSOCIATED WITH

More common

- Excess vegetable intake

Less common

- Nephrotic syndrome
- Diabetes mellitus
- Hypothyroidism
- Hyperlipidaemia
- Porphyria
- Anorexia nervosa
- Liver disease

MECHANISM/S

Results from carotene deposition in the stratum corneum.[55] This may occur through three main mechanism/s:

- excess intake of foods rich in beta-carotene
- hyperlipidaemia
- failure to convert carotene into vitamin A in the liver.

Carotene is found in many fruits and vegetables. It is absorbed and eventually converted to vitamin A. Carotene absorption is enhanced by lipids (beta lipoprotein in particular), bile acids and pancreatic lipase.[55] Thus, anything that increases absorption or decreases conversion to vitamin A may lead to hypercarotinaemia and carotenoderma (Table 7.7).

SIGN VALUE

Carotenoderma is considered harmless and finding the underlying cause is valuable only to avoid complications of that disease. For instance, carotenoderma may be the initial presentation of an eating disorder.

TABLE 7.7 Summary of mechanisms of carotenoderma/hypercarotinaemia

Condition	Mechanism
Nephrotic syndrome	Raised lipids in nephrotic syndrome enhance beta-carotene absorption
Diabetes	Hyperlipidaemia and impaired conversion of beta-carotene to vitamin A raises levels
Hypothyroidism	Hyperlipidaemia and impaired conversion of beta-carotene to vitamin A raises levels
Anorexia	Multiple suggested mechanism/s • Diet heavy in beta-carotene foods (e.g. carrots) • Acquired defect in metabolism of vitamin A[55] • Decreased catabolism of beta-lipoprotein[56]
Liver disease	Failure to convert beta-carotene to vitamin A

Hyperpigmentation and bronzing

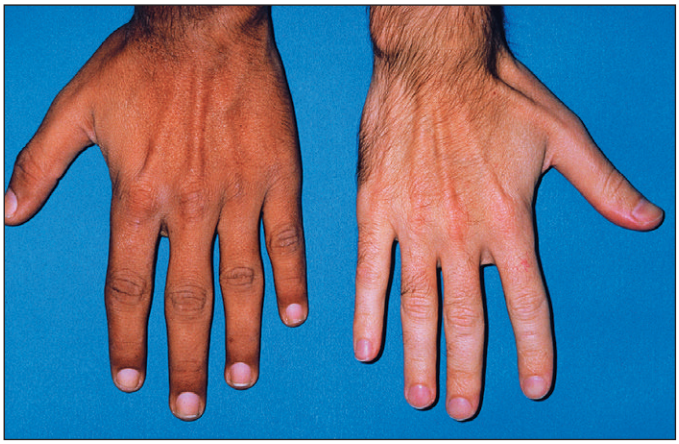

FIGURE 7.19 Hyperpigmentation seen in Addison's disease

Reproduced, with permission, from James WD, Berger TG, Elston DM (eds), *Andrews' Diseases of the Skin: Clinical Dermatology*, 11th edn, Philadelphia: Saunders, 2011: Fig 24-3.

DESCRIPTION

Two different terms with similar presentations and classically associated with different pathologies.

Haemochromatosis description

Hyperpigmentation of the skin, often described as a *bronzed and/or blue hue or slate grey*. Generally diffuse but the colour may be more pronounced on the face, neck and extensor surfaces.

Addison's disease description

Diffuse 'tanning' of the body – especially sun-exposed areas, bony prominences, skin folds, scars and extensor surfaces.

CONDITION/S ASSOCIATED WITH

- Addison's disease (ACTH-dependent causes) – very common
- Cushing's disease (ACTH-dependent causes) – less common
- Haemochromatosis

MECHANISM/S

Addison's disease

ACTH activates melanocyte-stimulating hormone (MSH) receptors on melanocytes, which, in turn, secrete melanin, giving the skin a tanned appearance.

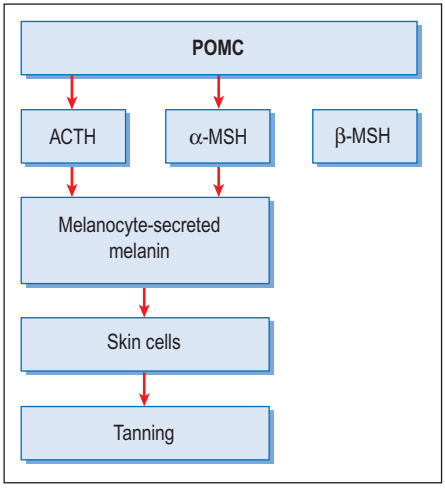

FIGURE 7.20 Mechanism of hyperpigmentation seen in Addison's disease

Pro-opiomelanocortin (POMC) is a precursor molecule from which two forms of MSH and ACTH are synthesised. One form of MSH, α-MSH, which is responsible for skin tanning, is identical to ACTH in the first 13 amino acids. Owing to this similarity, it is thought that ACTH is able

to stimulate melanocytes to produce melanin, which is then taken up by skin cells to produce the characteristic darkening.

Cushing's disease

In Cushing's disease, in which ACTH is secreted by pituitary tumours, tanning may occur by stimulation of melanocytes in a similar process to Addison's disease.

Haemochromatosis

Two separate mechanisms contribute to the characteristic hyperpigmentation in haemochromatosis. These are: 1) *haemosiderin deposition in the skin* and 2) *increased melanin production.*

Haemochromatosis is a disease of excess iron absorption. The excess iron may be deposited in a variety of organs, including the skin. When deposited in skin, haemosiderin changes the pigment, giving it a blue hue.

The change in pigmentation is also due to excess iron irritating the dermal tissue and inducing inflammation. This inflammation stimulates melanin production.

SIGN VALUE

Hyperpigmentation is a valuable sign. It is seen in 92% of patients with primary adrenocortical insufficiency and is one of the earliest manifestations of the condition.[2] It is also valuable in differentiating between primary and secondary adrenocortical insufficiency. In secondary adrenocortical insufficiency (caused by damage to the pituitary gland), ACTH is not secreted and, therefore, hyperpigmentation does not occur.

In Cushing's disease, it is seen less regularly, in 4–16% of patients,[57] so the negative predictive value is low. If present, it is valuable in localising the pathology in the hypothalamic axis. As in Addison's disease, hyperpigmentation is ACTH-dependent so, if it is present, the causes of Cushing's syndrome are narrowed to those that produce ACTH (see the box below).

USING HYPERPIGMENTATION TO HELP LOCALISE THE PROBLEM IN ENDOCRINOLOGICAL DISORDERS

As explained above, hyperpigmentation is a valuable sign you can use to localise the cause of both Addison's disease and Cushing's syndrome. Hyperpigmentation helps identify whether excess ACTH is present or not. In short:

Suspected Addison's + hyperpigmentation?

Think: damage to the adrenal gland (primary adrenocortical insufficiency)

- Autoimmune – most common in developed countries
- Metastatic malignancy
- Adrenal haemorrhage
- Infectious – TB (most common in developing countries), CMV, HIV
- Adrenoleukodystrophy
- Congenital adrenal hyperplasia
- Drugs (e.g. ketoconazole)

Suspected Cushing's syndrome + hyperpigmentation?

Think: ACTH-dependent excess cortisol

- Pituitary adenoma
- Ectopic ACTH (non-pituitary neoplasm)
- Ectopic CRH secretion (rare)

Hyperreflexia

DESCRIPTION

Used to describe exaggeration of normal reflexes.

CONDITION/S ASSOCIATED WITH

- Hyperthyroidism
- Upper motor neuron lesions (see Chapter 5, 'Neurological signs')

HYPERTHYROID MECHANISM/S

The mechanism is not understood. It is probably related to increased sensitivity to catecholamines due to excess thyroid hormone.

Hyperthyroid tremor

DESCRIPTION

A high-frequency, low-amplitude tremor seen in the hands, face and head that worsens on movement. It is quite fine in appearance and supra-physiological.

CONDITION/S ASSOCIATED WITH

- Hyperthyroidism

MECHANISM/S

The tremor is thought to be a result of increased sympathetic activity due to excess thyroid hormone inducing a boost in beta-adrenergic sensitivity and activity.[58]

SIGN VALUE

It is seen in up to 69–76%[41,59] of patients with hyperthyroidism with a specificity of 94%[41] and PLR of 11.4. If present in a patient with suspected hyperthyroidism, it is a valuable sign.

Hyporeflexia/delayed ankle jerks (Woltman's sign)

DESCRIPTION

Delayed or slower-than-normal reflexes, in particular a slow relaxation phase of the reflex.

CONDITION/S ASSOCIATED WITH

- Hypothyroidism
- Multiple neurological conditions (see Chapter 5, 'Neurological signs')
- Anorexia nervosa
- Advanced age
- Drugs (especially beta-blockers)
- Hypothermia

MECHANISM/S

In hypothyroidism, hyporeflexia is thought to be related to decreased muscle levels of myosin ATPase, causing a delay in muscle contraction[60] and a slowing in the rate of calcium re-accumulation in the sarcoplasmic endoplasmic reticulum,[61] which is needed for normal muscle contraction and relaxation.

SIGN VALUE

There are mixed reports on the value of the reflex (in particular Achilles reflex) as a diagnostic sign for hypothyroidism and for hyperthyroidism.

The half-relaxation time in well people is approximately 240 to 320 ms.[62]

- One study found 75% of hypothyroid patients had a delayed relaxation phase, with a PPV of 72.
- Another study found 91% of patients with hyperthyroidism and 100% of hypothyroid patients had a half-relaxation time outside the normal range, suggesting a very high sensitivity of the test.[63]
- Other studies[64] found up to 35% of hyperthyroid and 12% of hypothyroid patients were in the normal range.

All of these studies were completed using specialised recording devices that would not be routinely used in day-to-day practice. Furthermore, having readily available thyroid function tests makes this test less applicable in today's practice in isolation from other signs or symptoms.

Hypotension

DESCRIPTION

Abnormally low blood pressure, usually less than 100 mmHg systolic.

CONDITION/S ASSOCIATED WITH

- Addison's disease
- Hypothyroidism

MECHANISM/S

Numerous causes, see Chapter 3, 'Cardiovascular signs'.

Addison's disease

Dehydration and volume loss is the primary cause of hypotension in Addison's disease.

Mineralocorticoids regulate sodium retention and potassium excretion in the urine, sweat, saliva and GI tract. A deficiency of mineralocorticoids and, to a much lesser extent, corticosteroids leads to *salt wasting* and *failure to concentrate urine,* thus producing *decreased circulatory volume, dehydration* and *hypotension*.

Deficiency of glucocorticoids (adrenaline) may also lower the basal tone of the vasculature and, hence, resting systolic blood pressure.

SIGN VALUE

A common sign in acute primary adrenal insufficiency – up to 88% of patients exhibit hypotension.[2] However, given the myriad causes of hypotension, its value as an isolated sign is limited. Conversely, the presence of *hyper*tension is a strong negative predictor of a diagnosis of Addison's disease.[65,66]

Macroglossia

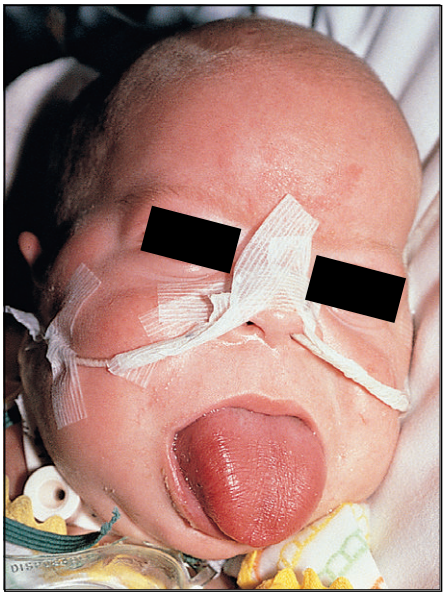

FIGURE 7.21 Macroglossia in an infant

Reproduced, with permission, from Eichenfield LF et al, *Neonatal Dermatology*, 2nd edn, Philadelphia: Saunders, 2008: Fig 27-11.

TABLE 7.8 Causes of macroglossia by mechanism

Tissue overgrowth
Beckwith–Wiedemann syndrome Acromegaly Hypothyroidism
Abnormal deposition/infiltration
Lymphatic malformations Hypothyroidism Neoplasms Storage diseases Amyloidosis Syphilis Tuberculosis
Inflammation
Hereditary angio-oedema Anaphylactic reaction Direct trauma
Relative/pseudomacroglossia
Down syndrome

DESCRIPTION

Enlargement of the tongue disproportionate to jaw and oral cavity size. Also can be described as a resting tongue that protrudes beyond the teeth or alveolar ridge.

True macroglossia is defined as macroglossia with characteristic hypertrophied or hyperplastic histological findings. Pseudomacroglossia is said to be tongue enlargement seen in relation to a small mandible but also with histological abnormalities.[67]

CONDITION/S ASSOCIATED WITH

There is a plethora of conditions that may cause apparent or actual macroglossia. These include, but are not limited to:

More common

- Hypothyroidism – in children
- Beckwith–Wiedemann syndrome – in children
- Down syndrome
- Lymphangioma – in children
- Haemangioma – in children
- Idiopathic hyperplasia – in children
- Metabolic disorders – in children
- Amyloidosis (both primary and secondary disorders) – most common cause in adults
- Acromegaly
- Traumatic

Less common

- Triploid syndrome
- Neurofibromatosis
- Syphilis
- Tuberculosis

MECHANISM/S

Most of the individual mechanisms for each condition are unclear. In simple terms, the cause can be put down to: *deposition of abnormal proteins/tissue* into the tongue, *overgrowth/hypertrophy* of normal tongue tissue and inflammation and swelling of the tongue. A summary of the causes and basic mechanisms can be seen in Table 7.8 and is discussed below.

Beckwith–Wiedemann syndrome

An abnormality on chromosome 11 leads to excess growth of normal structures and tissue, including tongue tissue.

Hypothyroidism

Thought to be as a result of *myocyte hypertrophy and deposition of myxoedema*, which leads to accumulation of fluid.[68,69]

Amyloidosis

In primary or secondary amyloidosis, there is excess production of an abnormal protein (amyloid). This protein can be *deposited in the tongue tissue*, leading to macroglossia.

Acromegaly

Acromegaly is a disorder of excess growth hormone, which stimulates a further excess of insulin growth factor. It is thought that these growth factors stimulate hypertrophy of various tissues, including the tongue, leading to hypertrophy and macroglossia.

Lymphangioma

Lymphangioma is a malformation and hyperplasia of the lymphatic system. When this occurs near or results in *deposition into the tongue* tissue, macroglossia may ensue.

SIGN VALUE

There are few evidence-based reviews on the value of macroglossia as a sign. However, if it is seen, it will almost always be pathological and investigation as to the cause is needed.

Necrobiosis lipoidica diabeticorum (NLD)

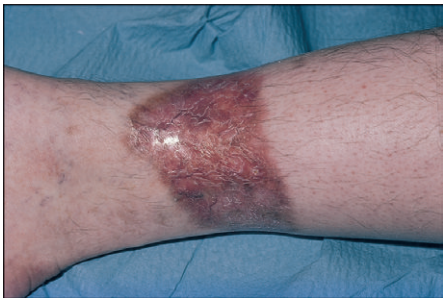

FIGURE 7.22 Necrobiosis lipoidica diabeticorum

Reproduced, with permission, from Swartz MH, *Textbook of Physical Diagnosis*, 6th edn, Philadelphia: Saunders, 2009: Fig 15-15.

DESCRIPTION

One or more sharply demarcated yellow-brown plaques on the anterior pretibial region.

CONDITION/S ASSOCIATED WITH

- Diabetes

MECHANISM/S

The mechanism has not been elicited.

It is known that NLD is a chronic granulomatous inflammatory disorder, with connective tissue degeneration; however, its link to glucose level and mechanism has not been established.[70]

Theories include:

- a form of immune-mediated vasculitis
- abnormal collagen deposition
- microangiopathy
- impaired neutrophil migration.

SIGN VALUE

One older study showed a strong association with autoimmune (type 1) diabetes, whereby almost two-thirds of patients with lesions had diabetes and 5–10% had glucose tolerance abnormalities.[71]

A more recent study showed only 11% of patients with NLD had diabetes,[16] and the prevalence of NLD in patients with diabetes was only 0.3–3.0%.[71]

Onycholysis (Plummer's nail)

FIGURE 7.23 Onycholysis – separation of the distal nail bed

Reproduced, with permission, from Habif TP, *Clinical Dermatology*, 5th edn, Philadelphia: Mosby, 2009: Fig 25-29.

DESCRIPTION

Separation of the nail plate from the nail bed.

CONDITION/S ASSOCIATED WITH

More common

- Trauma
- Infection
- Psoriasis

Less common

- Hyperthyroidism
- Sarcoidosis
- Connective tissue disorders

MECHANISM/S

The mechanism, aside from trauma, is unclear.

SIGN VALUE

There is little evidence of the prevalence of onycholysis in hyperthyroid patients. Other signs and symptoms are likely to present themselves prior to onycholysis.

Pemberton's sign

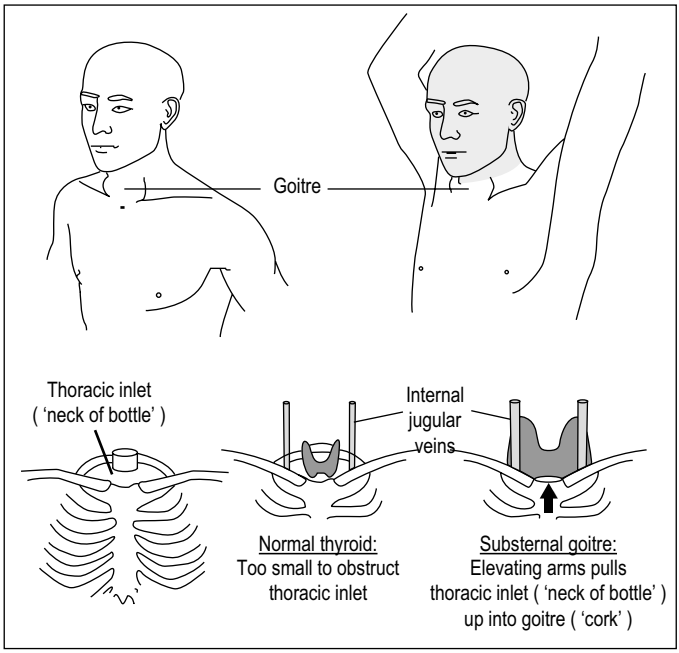

FIGURE 7.24
Pemberton's sign

Reproduced, with permission, from McGee S, *Evidence-Based Physical Diagnosis*, 2nd edn, Philadelphia: Saunders, 2007: Fig 22-6.

DESCRIPTION

The development of facial flushing, neck distension, engorged neck veins, stridor and raised JVP when a patient raises and holds the arms above the head.

CONDITION/S ASSOCIATED WITH

- Retrosternal/substernal goitre – common
- Tumour

MECHANISM/S

When the arms are raised, the ring of the thoracic inlet is brought upwards and gets stuck on the goitre. The goitre is said to 'cork' the thoracic inlet and, in doing so, compresses the adjacent internal jugular veins.

Blood backs up, causing distension of the neck veins and facial plethora. Stridor occurs with pressure on the upper airway from any mass, be it tumour or goitre.

SIGN VALUE

The frequency of Pemberton's sign is unknown in patients with substernal goitres.[23]

Periodic paralysis

DESCRIPTION

Periodic paralysis presents as episodes of painless muscle weakness that are often sudden and associated with preserved consciousness. Proximal muscles are affected more than distal muscles, and reflexes are decreased or absent. Periodic paralysis is associated with *hypokalaemia*.

CONDITION/S ASSOCIATED WITH

- Hyperthyroidism
- Congenital – most forms

MECHANISM/S

Defects in muscle ion channels are the key cause of thyrotoxic periodic paralysis, although the how or why is unclear.[72]

Hyperthyroidism increases the activity of the Na^+/K^+ pumps on muscle cells, producing a large and rapid shift of potassium intracellularly and leading to hyperpolarisation and absent muscle cell depolarisation.

SIGN VALUE

It is a rare event affecting between 2% and 20%, and 0.1% and 0.2%, in Asian and American populations, respectively. There is no correlation between severity of hyperthyroidism and the manifestation of paralysis.[73]

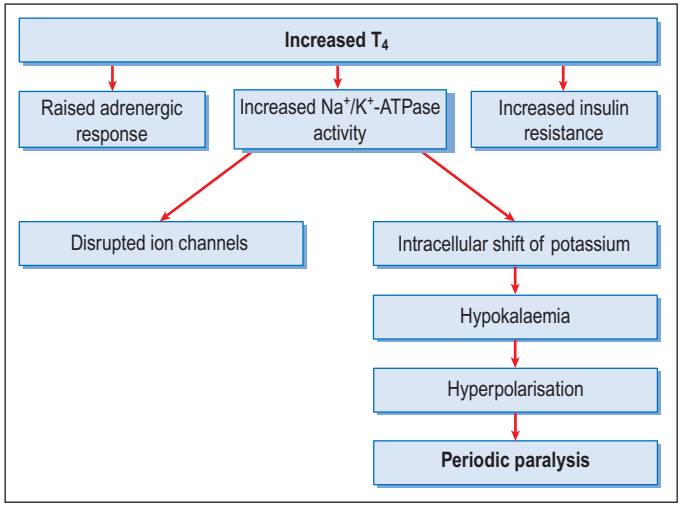

FIGURE 7.25 Mechanism of periodic paralysis in hyperthyroidism

Based on Radulescu D, Parv A, Pripon S et al, Endocrinologist 2010; 20(2): 72–74.

Plethora

DESCRIPTION

An excess of blood in a part or, by extension, a red florid complexion.[37]

CONDITION/S ASSOCIATED WITH

More common

- Chronic alcoholism
- Cushing's disease
- Parenchymal lung disease
- Menopause

Less common

- Polycythaemia
- Hypernephroma
- SVC obstruction
- Mitral stenosis
- Carcinoid syndrome

GENERAL MECHANISM/S

Plethora can be caused by an increased volume of blood flow to the face, any factor that may dilate the blood vessels in the area or blood vessels being closer to the skin's surface.

Cushing's disease

In Cushing's disease excess cortisol causes degradation and atrophy of the epidermis and underlying connective tissue. This leads to apparent thinning of the skin and the appearance of facial plethora.[2]

Carcinoid syndrome

Excess serotonin release seen in carcinoid syndrome causes the dilatation of skin vessels and the appearance of plethora.

Mitral stenosis

Mitral stenosis leads to increased pressure from the left side of the heart. This leads to increased venule and venous pressure, engorging small capillaries and causing plethora.

Parenchymal lung disease

Parenchymal lung disease may cause raised pulmonary artery pressure and, therefore, pressure back to the right side of the heart and into the venous system. This, in turn, can increase venous pressure, causing engorgement of blood vessels in the face.

SIGN VALUE

Seen in 70% of patients with Cushing's syndrome,[2] plethora has only limited specificity given its many possible aetiologies.

Polydipsia

DESCRIPTION

Although strictly more a symptom than a sign, excessive drinking can be witnessed and is often linked to polyuria. Polydipsia is the chronic excessive sensation of thirst and intake of fluid.[37] Differentiation should be made between true thirst due to dehydration-causing polyuria and that due to a dry mouth alone (due to effects of drugs or local factors).

CONDITION/S ASSOCIATED WITH

More common

- Diabetes mellitus
- Diabetes insipidus
- Anticholinergics

Less common

- Hypercalcaemia
- Psychogenic polydipsia
- Sjögren's syndrome
- Primary hyperaldosteronism

MECHANISM/S

Often secondary to polyuria and as a response to dehydration (from diabetes mellitus, diabetes insipidus, hypercalcaemia). See 'Polyuria' in this chapter.

Sjögren's syndrome

In Sjögren's syndrome, an autoimmune disorder stops the production of saliva (and affects lacrimal glands). The result of this is a dry mouth, and the patient continues to drink in order to alleviate the discomfort.

Psychogenic polydipsia

This is thought to be a multi-factorial malfunction of the hypothalamic thirst centre, involving the chronic intake of excessive amounts of water, which reset the thirst and ADH cue points. In other words, patients need to drink more to satisfy their feeling of thirst and/or ADH is inappropriately suppressed.

Positive symptoms of schizophrenia, compulsive behaviour, stress reactions, drinking to counteract anti-cholinergic side effects to medications and elevated dopamine responses stimulating the thirst centre have all been suggested as possible triggers.

Primary hyperaldosteronism

Excess aldosterone leads to hypokalaemia, which, in turn, causes a decrease in aquaporin water tubules in the cortical collecting duct. With less water able to be reabsorbed, obviously more is excreted, leading to polyuria.

Polyuria

DESCRIPTION

Passing of a large volume of urine within a defined period of time.[37] Although not truly a sign, it has value in a number of endocrinological and renal conditions, and in some settings can be measured.

CONDITION/S ASSOCIATED WITH

More common

- Diabetes mellitus
- Diabetes insipidus
- Excess IV fluids
- Osmotic mannitol infusion, radiocontrast media, high-protein tube feeds
- Drugs (e.g. diuretics, lithium, caffeine)
- Post obstructive diuresis

Less common

- Hypokalaemia
- Hypercalcaemia
- Psychogenic polydipsia (e.g. schizophrenia)
- Excess IV fluids
- Cushing's syndrome
- Primary hyperaldosteronism
- Inability to concentrate urine: sickle cell trait or disease, chronic pyelonephritis, amyloidosis

MECHANISM/S

Polyuria often develops from two key mechanisms: osmotic load and excretion of free water.

1. In some conditions, there is a high 'osmotic load' of the serum being filtered through the kidney due to the *excretion of non-absorbable solutes (e.g. glucose)*. This leads to an *osmotic diuresis*. Put simply, this means large quantities of bigger solutes in the renal tubules of the kidney hold water 'in', rather than allowing it to be reabsorbed. In addition, the concentration gradient in the proximal tubules is altered, affecting sodium reabsorption and urine concentration.
2. The second main mechanism is an *inappropriate excretion of free water*,[74] which is usually due to abnormalities in vasopressin production or in response to vasopressin plus an inability to concentrate urine.

Diabetes mellitus

Polyuria in diabetes mellitus is due to *osmotic diuresis* from excretion of excess glucose. Water is drawn out by osmosis due to the high filtration of glucose in the kidney. Polyuria in this setting indicates symptomatic hyperglycaemia.

Diabetes insipidus

Diabetes insipidus (DI) can be further broken down into central and peripheral types. Nephrogenic DI can be further classified as either congenital or acquired. The basic mechanisms are shown in Table 7.9.

Post obstructive diuresis

Seen when bilateral urinary tract obstruction is relieved and thought to be due to:

1. the excretion of retained urea, causing an osmotic diuresis
2. obstruction of ureters raising pressure in the tubules of the kidney and impairing sodium chloride reabsorption. With less sodium being reabsorbed, concentration gradients in the kidney are not maintained and water is lost with sodium chloride.

Lithium

Lithium has a number of effects on the kidney. Its mechanism in causing polyuria is hypothesised to be by impairing the stimulatory effect of ADH on adenylate cyclase[75] that, when present, normally leads to the production of water channels in the cortical collecting duct.

Other effects lithium may have include:

- partially inhibiting the ability of aldosterone to increase ENAC expression and salt reabsorption; as a consequence, salt is lost in the urine and water follows it out[76]
- potentially inhibiting sodium reabsorption in the cortical collecting channel; decreased sodium reabsorption leads to salt wasting and water follows the sodium out in the urine.[77]

TABLE 7.9 Mechanisms of diabetes insipidus (DI)

	Abnormality	Mechanism
CENTRAL DI	Idiopathic or secondary to any disorder that leads to damage to the vasopressin (ADH)-secreting neurons in the posterior pituitary	Inadequate excretion of ADH from the pituitary → inadequate activation of the V2 receptors and aquaporins → water is not reabsorbed and is lost in urine
CONGENITAL NEPHROGENIC DI	Mutation of V2 receptor on distal tubule of the kidney	V2 receptor is not responsive to ADH stimulation → failed activation of aquaporin channels → water not appropriately retained and so lost in urine
	Mutation of aquaporin water channel	Mutation of aquaporin water channel does not allow for adequate reuptake of water when the V2 receptor is stimulated by ADH. The water is excreted in urine
ACQUIRED NEPHROGENIC DI	Hypokalaemia	Hypokalaemia leads to decreased expression of aquaporin 2 channels → decreased water uptake and therefore increased diuresis
	Hypercalcaemia	Hypercalcaemia leads to decreased expression of aquaporin 2 channels → decreased water uptake and therefore increased diuresis

Polyuria: Cushing's syndrome

Excess glucocorticoids have been shown to inhibit osmosis-stimulated ADH secretion as well as directly enhancing free water clearance,[37] thus producing polyuria.

Hyperglycaemia causing osmotic diuresis is rarely the cause of polyuria in Cushing's syndrome.

PSYCHOGENIC POLYURIA MECHANISM/S

Seen in concert with psychogenic polydipsia; see 'Psychogenic polydipsia mechanism/s' under 'Polydipsia' in this chapter.

Pre-tibial myxoedema (thyroid dermopathy)

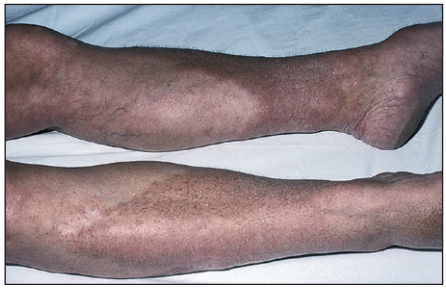

FIGURE 7.26 Pre-tibial myxoedema

Reproduced, with permission, from Kanski JJ, *Clinical Diagnosis in Ophthalmology*, 1st edn, Philadelphia: Mosby, 2006: Fig 2-35.

DESCRIPTION

Thickening of the skin limited to the pre-tibial area. However, as the thickening may occur in other areas, the term 'thyroid dermopathy' is more correct.

CONDITION/S ASSOCIATED WITH

- Graves' disease

MECHANISM/S

The mechanism behind pre-tibial myxoedema is similar to (or an extension of) that seen in Graves' ophthalmopathy. *Immunological, cellular* and *mechanical factors contribute* to the production and localisation of glycoaminoglycans and the sequestration of fluid to produce the characteristic skin changes.

In Graves' disease, lymphocytes infiltrate the dermal tissues around the pre-tibia.[78] It is also hypothesised that in Graves' disease there is an over-expression of TSH receptors at certain sites, including the pre-tibial area. These receptors are stimulated by antibodies produced by local immune cells, which lead to fibroblast secretion of glycoaminoglycans and the sequestration of fluid.

Mechanical forces play a role in the localisation of the skin changes.[79–81] Dependent oedema, produced by reduced lymphatic return, increases the pooling of disease-related cytokines and chemokines and other factors that increase the effect[82] in the immediate area, producing the characteristic skin changes.

SIGN VALUE

Pre-tibial myxoedema is a rare sign clinically and is almost always preceded by the more common eye signs of Graves' disease. It is seen in 0.5% to 4.3% of patients with a history of thyrotoxicosis and in up to 13% of patients with Graves' ophthalmopathy,[78,83] Interestingly, forearm changes of so-called pre-tibial myxoedema are commonly present in cases of clinically definite Graves' disease, and can be detected by ultrasound as skin thickening.

Prognathism

DESCRIPTION

Abnormal protrusion of one or both jaws, particularly the mandible, relative to the broader facial skeleton.[37]

CONDITION/S ASSOCIATED WITH

- Congenital defects
- Acromegaly

MECHANISM/S

The final mechanism of prognathism in acromegaly is complex and unclear. It is related to the excess production of *growth hormone and insulin-like growth factor-1, causing excess bone growth in the jaw.*

In acromegaly, there is an *excess production of growth hormone* (GH) from the anterior pituitary gland. GH has effects on body tissues both directly and indirectly through the stimulation of insulin-like growth factor-1 (IGF-1). Both IGF-1 and GH affect chondrocytes and can cause excess production. Disproportionate growth of the mandible stimulated by a surplus of GH and IGF-1 may contribute to prognathism in patients with acromegaly.

SIGN VALUE

Prognathism virtually never occurs in acromegaly in isolation, so its value as a diagnostic sign is limited. Conversely, if no other signs associated with acromegaly are present, congenital abnormality is the most likely cause.

Proximal myopathy

DESCRIPTION

Weakness of the proximal muscles of the girdle including the quadriceps and biceps. Can be easily demonstrated by asking the patient to rise from a seat and/or to pretend to be brushing their hair or hanging washing on the clothes line.

CONDITION/S ASSOCIATED WITH

Many potential causes including, but not limited to:

More common

- Hyperthyroidism
- Hypothyroidism
- Cushing's syndrome
- Peripheral neuropathies
- Polymyalgia rheumatica

Less common

- Hyperparathyroidism
- Sarcoidosis
- Coeliac disease
- Polymyositis
- Dermatomyositis
- Genetic muscular dystrophies

MECHANISM/S

Hyperthyroid

The mechanism is unclear. Possible contributing factors include:[84–87]

- increased cellular metabolism and energy utilisation
- increased catabolism and protein degradation
- inefficient energy utilisation
- disturbance of the function of muscle fibres due to increased mitochondrial respiration
- accelerated protein degradation and lipid oxidation
- enhanced beta-adrenergic sensitivity.

Hypothyroidism

Lack of thyroid hormone slows normal metabolic function, including protein turnover-impaired carbohydrate metabolism.[88,89] As a consequence, muscle cells do not have nor utilise energy as efficiently, resulting in weakness.

Hyperparathyroidism

The mechanism is unclear.

It is known that PTH does impact on skeletal muscle but, given that the variables it affects include calcium, phosphate and vitamin D, it is difficult to pinpoint the exact cause of the proximal muscle weakness.[83]

Cushing's syndrome

The catabolic effects of glucocorticoids *break down proteins in the muscle fibres,* causing weakness. Additional factors include hypokalaemia and physical inactivity.

In some cases *hypokalaemia*, caused by excess mineralocorticoids causing potassium excretion via the kidney, may exacerbate the situation. This is caused by an imbalance in the electrochemical gradient between the intracellular and extracellular spaces. Simply put, a gradient of potassium is required between the two spaces, in order for cells to effectively 'fire' – i.e. depolarise and repolarise. Decreasing the potassium outside a cell causes *hyper-polarisation of the cell*, making it *harder* for the cells (in this case proximal skeletal muscle fibres) to fire.

Physical inactivity of patients with Cushing's syndrome also plays a role.

SIGN VALUE

Seen in 60–80% of patients with hyperthyroidism, but also seen in numerous other endocrinological and other disorders. It is not common for proximal myopathy to be an initial presentation of hyperthyroidism.

In hypothyroidism, it is seen in 30–80% of patients and, therefore, has only moderate sensitivity and low specificity.

Skin tags (acrochordon)

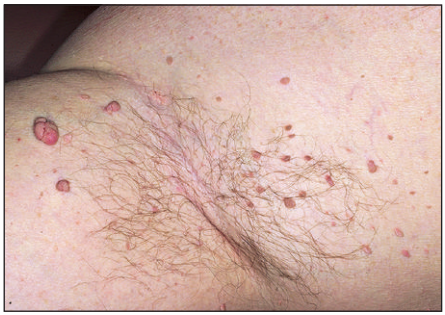

FIGURE 7.27 Skin tags

Reproduced, with permission, from Habif TP, *Clinical Dermatology*, 5th edn, Philadelphia: Mosby, 2009: Fig 20-17.

DESCRIPTION

Pedunculated papules or nodules that are most commonly located on the eyelids, neck and axillae.[90]

CONDITION/S ASSOCIATED WITH

- Normal variant
- Diabetes
- Acromegaly

MECHANISM/S

The mechanism is unclear.

Theories have included:

- frequent irritation
- normal ageing process
- hormone levels (e.g. high levels of growth hormone in acromegaly).

SIGN VALUE

Of limited value, as skin tags are very common in the general population. It has been claimed the incidence is greater in diabetic, obese patients as well as those with acromegaly. Interestingly, however, recent studies have shown an association between the presence of skin tags and insulin resistance.[91,92] In addition, a small study has suggested that skin tags are increased in patients with metabolic derangements and may present as a risk marker of cardiovascular disease and atherosclerosis.[93]

Steroid acne

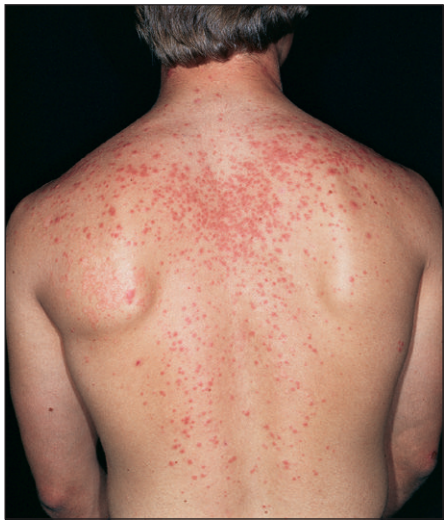

FIGURE 7.28 Steroid-induced acne

Reproduced, with permission, from Habif TP, *Clinical Dermatology*, 5th edn, Philadelphia: Mosby, 2009: Fig 7-33.

DESCRIPTION

Steroid acne differs from normal acne vulgaris in that it is of uniform size and symmetric distribution and is usually present on the neck, chest and back. It is typically flesh or pink-to-red coloured, with dome-shaped papules and pustules.

CONDITION/S ASSOCIATED WITH

More common

- Endogenous and exogenous androgen sources
- Diabetes
- Drug therapy

Less common

- Hodgkin's disease
- HIV infection

MECHANISM/S

Steroid excess in Cushing's syndrome may exacerbate existing acne; however, it may more often be an acne-like condition called malassezia (pityrosporum) folliculitis.[94] This is characterised by an alteration in normal skin conditions, including changes to immunity, sebum production and the growth of normal skin flora.[95] The end result is plugging of the hair follicle and an environment that allows a particular yeast (*Malassezia furfur*) to proliferate.

In Cushing's disease, it is possible that alterations of immunity caused by corticosteroid excess will allow fungal proliferation.

High levels of androgens and sebum production may also contribute.

Trousseau's sign

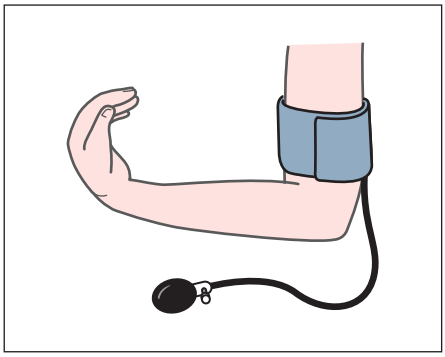

FIGURE 7.29 Trousseau's sign

DESCRIPTION

After inflating a blood pressure cuff above systolic blood pressure and leaving it on the patient for 3 minutes, muscular contraction – including flexion of the wrist and MCP joints, hyperextension of the fingers and flexion of the thumb on the palm – occurs (see Figure 7.29).

CONDITION/S ASSOCIATED WITH

More common

- Hypocalcaemia of any cause:
  - Hypoparathyroidism
  - Low vitamin D
  - Pseudohypoparathyroidism
  - Pancreatitis
- Hyperventilation/respiratory alkalosis

Less common

- Hypomagnesaemia

MECHANISM/S

See 'Chvostek's sign' in this chapter for an explanation of the increased neuronal excitation or tetany seen in conditions associated with the sign. By inducing ischaemia in the arm through the cuff, neuronal excitation (and hence muscular contraction) is exaggerated, producing the characteristic sign.

SIGN VALUE

1–4% of normal patients will have a positive Trousseau's sign; however, it is more specific than Chvostek's sign for latent tetany and hypocalcaemia.

Uraemic frost

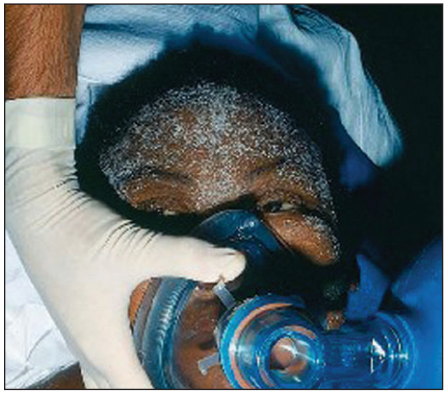

FIGURE 7.30 Uraemic frost

Reproduced, with permission, from Marx JA, Hockberger RS, Walls RM et al (eds), *Rosen's Emergency Medicine*, 7th edn, Philadelphia: Mosby, 2009: Fig 95-4.

DESCRIPTION

Fine white or yellowish 'frost' on the skin.

CONDITION/S ASSOCIATED WITH

- Renal failure

MECHANISM/S

In renal failure that is unmanaged, blood urea levels rise to such an extent that the urea content in sweat also mounts. Normal evaporation of sweat plus high urea concentration results in crystallisation and deposition of the urea on the skin.

SIGN VALUE

With early dialysis, uraemic frost is a very rare occurrence in developed countries.

Vitiligo

DESCRIPTION

A chronic disorder of the skin, usually progressive, consisting of depigmented white patches often surrounded by a hyperpigmented border.[37]

CONDITION/S ASSOCIATED WITH

Autoimmune diseases including:

- Graves' disease
- Addison's disease
- Hashimoto's thyroiditis
- Pernicious anaemia
- SLE
- Inflammatory bowel disease

MECHANISM/S

The mechanism is not yet fully understood.

Destruction of dermal melanocytes occurs but how or why this happens is not clear. The many theories about possible causes of this destruction include autoimmune, cytotoxic, biochemical, oxidant–antioxidant, neural and viral mechanisms. Several studies also point to a significant role of genetic susceptibility to vitiligo.[96]

Studies have shown circulating antibodies to melanocytes in patients with vitiligo, and the levels of antibodies have been correlated with disease severity.[97] Similarly, auto-reactive cytologic T cells and certain inflammatory cytokines are seen at increased levels in patients with vitiligo and may play a role in their destruction.[98]

Other factors seen in vitiligo that are thought to contribute ultimately to the destruction of melanocytes include: oxidative stress,[96,98,99] neural disruption and increased levels of CMV and other viruses.[31]

SIGN VALUE

Seen in 20% of patients with primary adrenocortical insufficiency (Addison's disease).[100] It also clusters with pernicious anaemia.

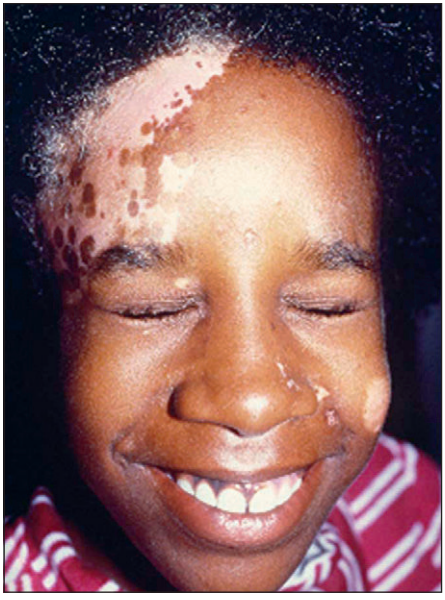

FIGURE 7.32 Vitiligo

Reproduced, with permission, from Anderson DM, *Dorland's Dictionary*, 30th edn, Philadelphia: Elsevier, 2003.

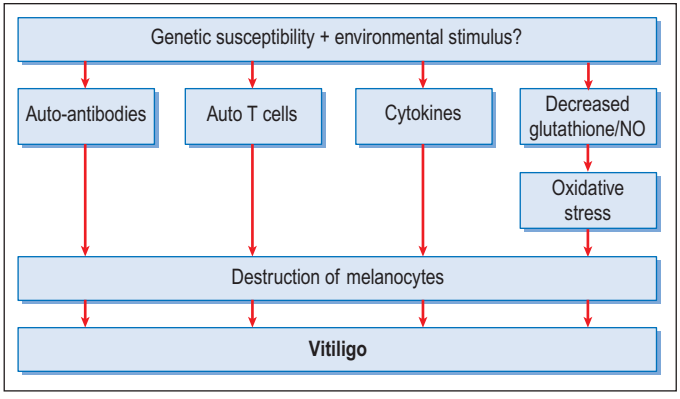

FIGURE 7.31 Mechanism of vitiligo

Webbed neck (pterygium colli deformity)

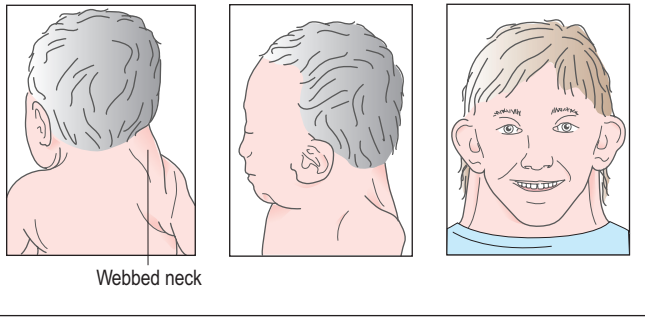

FIGURE 7.33 Webbed neck

DESCRIPTION

An accentuated skin fold that runs along the side of the neck to the shoulders.

CONDITION/S ASSOCIATED WITH

- Turner syndrome – all or one of the sex chromosomes absent
- Noonan syndrome – mutation of gene

MECHANISM/S

The mechanism is unclear. In Turner syndrome, there is an absence of all or part of one sex chromosome; it is not clear how this leads to a webbed neck.

In Noonan syndrome, nearly 50% of patients have a genetic mutation of a gene on chromosome 12 that modulates cellular differentiation and proliferation.[6]

SIGN VALUE

An uncommon sign and, if truly present, a webbed neck is almost always pathological.

In Turner syndrome, up to 40% of females will have a webbed neck.[6]

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