MACULAR EDEMA

Macular Edema

Conference Proceedings of the 2nd International Symposium on Macular Edema, Lausanne, 23–25 April 1998

Edited by

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Preface

Conference Proceedings of the 2nd International Symposium on Macular Edema, Lausanne, 23–25 April 1998

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From 23 to 25 April 1998 the 2nd International Symposium on Macular Edema was held at the Olympic Museum in Lausanne, Switzerland. This meeting followed in the footsteps of the 1st International Symposium on Macular Edema which had united a distinguished group of scientists and clinicians in 1983 under the chairmanship of the late Professor Paul Henkind. In the editorial of the published collected papers of this symposium Henkind had expressed his vision for future discoveries concerning macular edema with the words 'Some day all of the diversity of views expressed will undoubtedly coalesce, just as the small cysts in time may form a single large cyst. At that point, one brief cohesive paper should be sufficient to encompass the topic with absolute clarity'.

Over 14 years have since passed and we are still striving towards this goal. A multitude of new aspects concerning the pathogenesis, the imaging techniques and the treatment of macular edema have emerged as a result of relentless research activities around the globe, and the timely reunion in Lausanne brought together once again both eminent clinicians and scientists to discuss these more recent developments over the course of two days.

The present compilation of manuscripts represents the quintessence of papers given at this meeting. We have organized the material into a first part covering basic scientific aspects with a series of review papers initiating the reader into the major issues of cellular mechanisms of the blood–retinal barrier and its breakdown associated with macular edema. This is complemented in the second part by clinical studies addressing particular issues of the pathogenesis and treatment of macular edema. We owe a great debt of gratitude to Professor Michael F. Marmor, Editor-in-Chief of Documenta Ophthalmologica, for his unfailing support in the production of this special supplementum. Special thanks are also due to Raquel Haakmat from Kluwer Academic Publishers who expertly shepherded the work through to its published form.

We trust that the material in this issue will be both a useful reference for future studies in macular edema research and a challenge to learn more.


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The historical discovery of macular edema

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Abstract. The occurence of macular edema, or of intraretinal fluid in general, was largely unknown prior to the invention of the ophthalmoscope. One of the first reports on 'Retinitis in Glycosuria', a disease complex, which today would partly be described as diabetic maculopathy, was published in 1856 by Jaeger. His observations were confirmed less than twenty years later by Nettleship in London, and in 1875 Appolinaire Bouchardat from Paris described fluid and lipid accumulation in the macula which led – in his words – to a glucose induced amblyopia. The first pathophysiological hypotheses of fluid accumulation in the posterior pole were then put forward in 1882 by Tartuferi, who thought the edema represented swelling of photoreceptor sheaths. In 1896, the Frenchman Nuel coined the term 'oedème maculaire' which he had observed in a retinitis pigmentosa patient. However, it was not until the end of the first World War, that the Swiss ophthalmologist Alfred Vogt observed macular edema in a variety of other ocular conditions such as iridocyclitis or retinal vein occlusion as well as the progression from macular edema to a macular hole. A quarter of a century later Bangerter coined the German term 'Zystoides Makulaödem', and in 1950, Hruby was the first to draw attention to the development of macular edema after cataract extraction. Three years later this was followed by Irvine's classical paper on cystoid macular edema after intra- and extracapsular cataract extraction which had been complicated by incarceration of the vitreous in the anterior segment with consecutive tugging on the macula. A decade later, the phenomenon of cystic fluid accumulation in the macula after cataract extraction was further characterised by Gass and Norton using fluorescein angiography. The ensuing years saw the emergence of new concepts regarding the blood-retinal barrier and the paramount role of its dysfunction in the development of macular edema.

Introduction

Looking back on the historical discovery of macular edema one can only be impressed by the wealth of data that was already known at the beginning of the twentieth century. The painstaking accumulation of clinical observations, and the meticulous drawings of different fundus lesions was so advanced that all the major causes of macular edema were already known and described in detail at the time of the first world war. The first reports were mainly concerned with diabetic macular changes. This was followed with the recognition of edema after trauma and in association with retinitis pigmentosa. After the turn of the century other causes for macular edema such as retinal vein occlusion, anterior and posterior segment inflammation and tumors were identified. All these discoveries were the direct consequence of technological advances

such as the perfection of the direct ophthalmoscope and also of fundus photography, which allowed the documentation of the retinal findings to become a more standardised procedure. The following historical review stands as an introduction to the present volume on macular edema, and as a humble tribute to the astute clinical observational skills displayed by ophthalmologists of the nineteenth and early twentieth century.

The pre-ophthalmoscopic era

Although detailed information on the clinical state of the retina was not available before the invention of the direct ophthalmoscope, some clinicians predicted the existence of retinal disease in the presence of a normal anterior segment already before 1850. As far as macular disease was concerned, these ideas were particularly put forward after the observation of patients who suffered from diabetes mellitus. The French ophthalmologist Appolinaire Bouchardat, for example, reported in 1846 the development of visual loss in the absence of anterior segment changes, notably the absence of cataract [1]. This loss of vision was partly reversible and amelioration was in most cases associated with better control of the diabetes in general. Similar observations were made a few years later by Bouchardat's countryman Tavignot [2]. However, no histo-pathological specimens were examined, and the implication of macular disease in diabetes remained speculative until the advent of the ophthalmoscope [3]. The revolution which this invention brought about was remarkable. For the first time it was now possible to observe the retina in a clinical setting allowing the detailed diagnosis of macular lesions. It comes therefore as no surprise that the impulses thus generated led in the ensuing fifty years to a tremendous increase in the knowledge of macular edema.

The advent of the ophthalmoscope and the discovery of diabetic maculopathy

One of the first reports on what today would be described as diabetic maculopathy was published in 1856 by Eduard Jaeger. Using the newly developed direct ophthalmoscope he put together one of the first atlases of ocular fundus pictures which were painstakingly drawn during an average of 20 clinical sessions per patient. In the macular region of one diabetic patient he was thus able to distinguish 'roundish or oval, yellowish spots and extravasations which permeate part or the whole thickness of the retina' [4]. Jaeger's findings were, however, controversial at the time, and Albrecht von Graefe openly claimed that there was no proof of a causal relationship between diabetes and

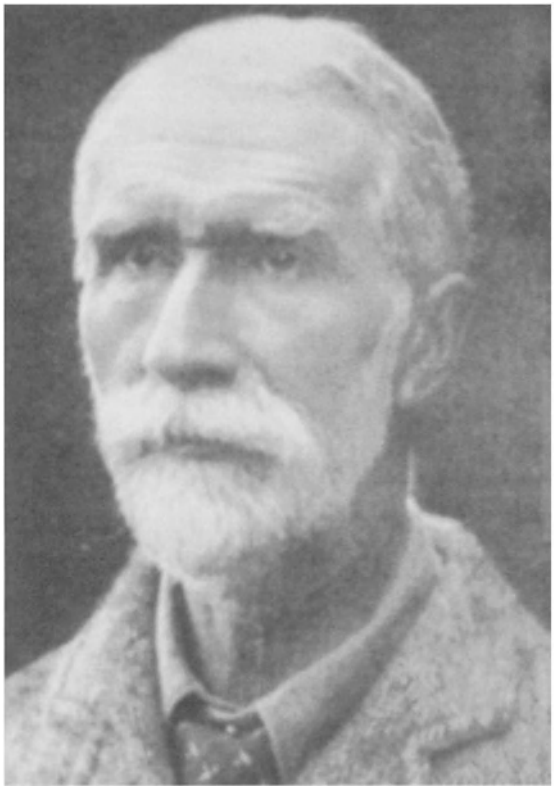


Figure 1. Eduard Nettleship F.R.S. (1845–1913) published the first report with histopathological proof of diabetic changes in the retina in 1872, which was followed by several other publications in this field. He remained on the staff of Moorfields Eye Hospital until his early retirement at the age of 57, after which he embarked on a new scientific career devoting his time and energy to the study of hereditary eye diseases. (From: The History of Moorfields Eye Hospital, London, 1929.)

retinal complications [5]. Given von Graefe's powerful influence on European ophthalmology at the time, many followed his credo, and – with the exception of a short report by the Frenchman Desmarres in 1858 [6] – further well documented data for the corroboration of a causal relationship between diabetes and maculopathy did not emerge until 1869 when Noyes published his report entitled 'Retinitis in glycosuria' in the United States [7]. During the same time detailed histological observations on a cystic degeneration unrelated to diabetes was recorded by the Russian ophthalmologist Iwanoff. Although he found these changes predominantly in the peripheral retina, several cases were reported where cystic spaces were found in the foveal area, although no association with other ocular or generalised diseases was mentioned [8].

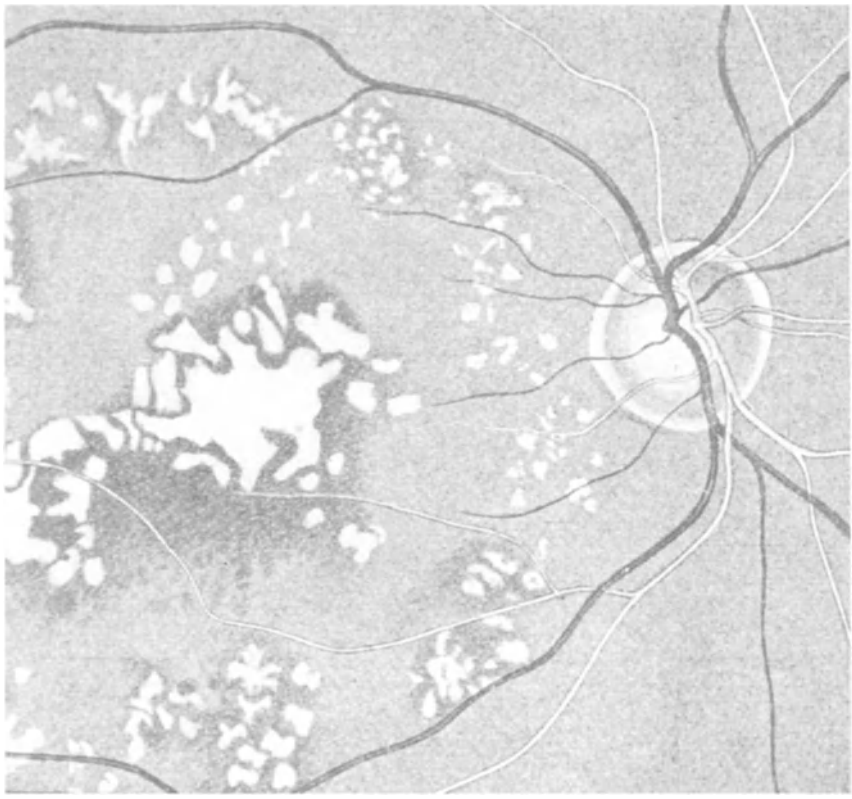
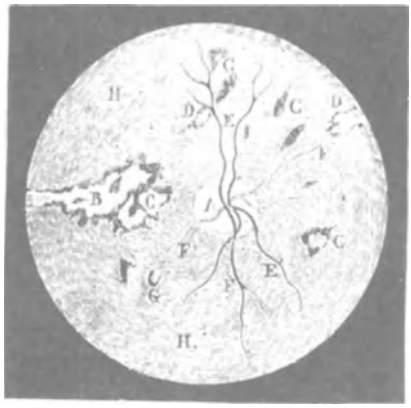


Figure 2. Fundus drawing of the right eye of one of Nettleship's original patients who was diagnosed with "diabetic retinitis". Note the multiple intraretinal whitish exsudates, which are confluent in the foveal region and which are sourrounded by a circinate ring. (From: Graefe-Saemisch Handbuch der Augenheilkunde, Berlin, 1914.)

Noyes's observations in diabetics were confirmed a few years later by Eduard Nettleship in London, who, in 1872, expanded on this theme in his seminal paper 'On oedema or cystic disease of the retina' [9]. Nettleship provided the first histopathological proof for a 'cystoid degeneration of the macula' in patients with diabetes. This was followed shortly afterwards by his report on 'Glycosuric retinitis' further delineating the pathological retinal changes induced by diabetes [10]. Nettleship was an impressive scientist and clinician (Figure 1). Professor of veterinary surgery at the age of 22, he later became curator of the pathology museum of Moorfields Eye Hospital during which time his seminal contributions to the understanding of diabetic retinal changes were produced (Figure 2). He later became senior surgeon at Moorfields and oculist to Queen Victoria. Nevertheless, at the height of his professional success, and aged only 57, he retired from all his professional



A, papille du nerf optique.
E, E, E, veines.
F, F, artères.
C, C, C, C, épanchements de sang, dessinés en noir
D, D, épanchements semblables au centre desquels on voit une tache blanche due à la résorption du pigmentum.
B, larges plaques blanches entourées d'un liseré de [illegible] que C, et qui paraît dû à un large [illegible] résorbé.
H, H, parties saines.

Figure 3. Jundus drawing of a right eye showing an advanced diabetic maculopathy. Note the presence of a large plaque of exsudates (B,C) in the macula as well as several small hemorrhages (C). (From: A Bouchardat *De la glycosurie ou diabète sucré*, Paris, 1875.)

positions in 1902, bequeathed a considerable amount of money to Moorfields Eye Hospital to buy new instruments and embarked – not as one might suspect on an easy life – but on another scientific career. During the next decade he devoted his newly found liberty and time to the study of ocular hereditary disease which led to several landmark articles and eventually to his election as a fellow of the Royal Society in 1912.

In 1875, the Frenchman Appolinaire Bouchardat from Paris, who had already hinted at a causal relationship of diabetes with retinal changes earlier [1], published his book 'De la glycosurie ou diabète sucré' in which he described fluid and lipid accumulation in the macula with detailed drawings of these changes (Figure 3). These deposits led – in his words – to a glucose induced amblyopia [11]. At the same time, the German ophthalmologist Theodor Leber published a whole series of clinical observations on what he called glycosuric retinitis [12], putting thus right the erroneous statement by his countryman von Graefe a few decades earlier. The first pathophysiologic hypotheses for the accumulation of fluid in the posterior pole were, however, not put forward until 1882, when Tartuferi proposed that the edema reflected a swelling of photoreceptor sheaths [13].

Discovery of macular edema in multiple ocular disorders

The majority of the initial reports on what today is called macular edema were mainly concerned with the diabetic etiology. However, from 1870 onwards other conditions became known that could induce similar changes at the fo-

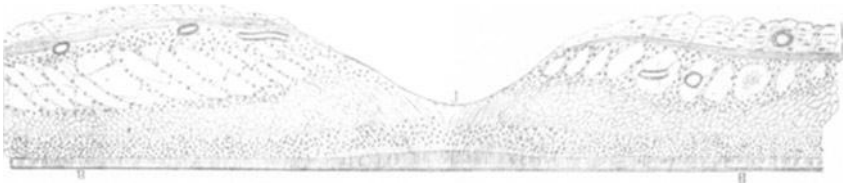


Figure 4. Histopathological specimen of the macular retina from a retinitis pigmentosa patient. Note the thinning of the photoreceptor layer. In Henle's layer multiple cysts are seen in the perifoveal region. The edema has also spilled into the inner nuclear layers. (From: J-P Nuel, *Oedème maculaire et périfovéal*, Arch d'Ophthalmol, 1896.)

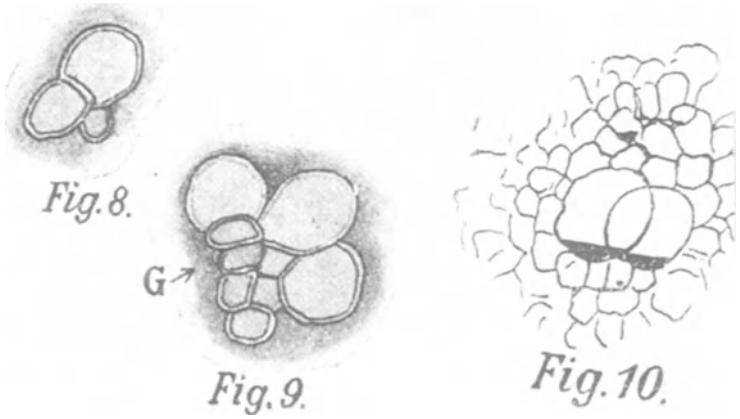


Figure 5. Original drawing from Vogt showing cystoid macular edema associated with bilateral acute iridocyclitis (Figure 8) showing an increase in the number of the cystic spaces 10 days later (Figure 9). The walls of some cysts have a yellowish tinge (arrow). Figure 10 shows macular edema 4 weeks after a central retinal vein occlusion. Note the two central cysts with horizontal blood levels. (From: A. Vogt, *Weitere ophthalmoskopische Untersuchungen im rotfreien Licht*. Klin Mbl Augenheilk, 1918.)

vea. In his classical description of retinal edema after trauma to the eye, Berlin published in 1873 experimental and histopathological data on the rabbit [14]. In 1896, the Frenchman Nuel coined the term 'Oedème maculaire' which he had observed in a histopathological specimen of a retinitis pigmentosa patient [15] (Figure 4). This observation was later confirmed clinically by Ginsberg [16]. Around the turn of the century, Birch-Hirschfeld drew attention to the development of macular edema after X-ray irradiation of the globe for a malignant melanoma [17], and Purtscher described in 1910 retinal hemorrhages with macular edema after severe head trauma [18]. The first photographic reproduction of cystoid macular changes was published in 1912 by Oguchi in Japan [19], clearly showing cystic spaces in the inner and outer nuclear as well as in the plexiform layers.

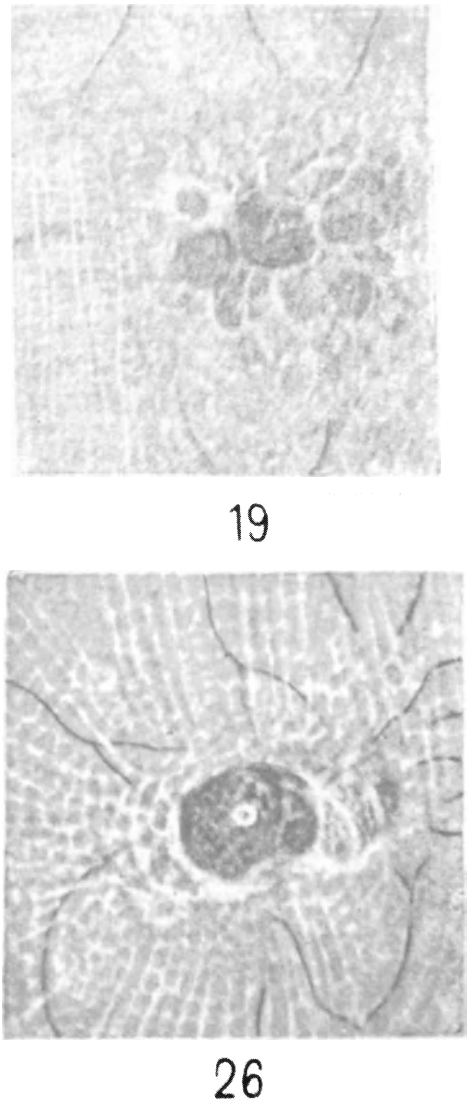


Figure 6. Original drawings from Vogt showing the different stages of macular hole formation in several cases of cystic macular edema. Note the different shapes of the holes and the residual cysts that encroach onto the fovea. (From: A. Vogt, *Ophthalmoskopische Untersuchungen der Macula lutea im rotfreien Licht*. Klin Mbl Augenheilk, 1921.)

An important landmark was reached just at the end of the first World War when the Swiss ophthalmologist Alfred Vogt published his two seminal papers. The first described a new technique to observe the macula using red-free light [20], which made it possible to diagnose very subtle changes, such as macular edema, at the level of the fovea. The second paper summarised in detail the appearance of macular edema in a variety of conditions such as iridocyclitis, retinal vein occlusion (even showing horizontal blood levels in the cysts), as well as the progression from macular cysts to a macular hole [21] (Figures 5 and 6). The inflammatory origin of macular edema had already been hinted at by Leber in 1877, but no clear word on the correlation was given [22].

After these landmark articles several scientists contributed to the literature on macular edema. Among them were Koyanagi, Lowenstein, Junius and others who described its occurence in many different vascular and inflammatory diseases [23]. However, again, one man stands out. Arthur James Ballantyne (1876–1954) chaired the opthalmology department of the university of Glasgow. He had contributed to no small degree to the literature on retinal diseases but it was not until his retirement in 1941 that he could devote all his time and energy to his lifelong interest: diabetic retinopathy. The most important work which he published in 1943 showed for the first time the role of capillary wall alterations in the development of diabetic retinopathy and maculopathy, as well as the presence of deep waxy exudates in the outer plexiform layer [24]. The last major review of the medical causes of macular edema was finally published by Bangerter in 1945 who coined the German term 'Zystoides Makulaödem' [25]. He advocated retrobulbar injection of Atropin as an effective therapy of the edema.

The discovery of cystoid macular edema after cataract extraction

With the increasing predominance of cataract surgery in the years after the second World War a hitherto unknown complication of this intervention became apparent in 1950. The Austrian ophthalmologist Karl Hruby from Vienna was the first to draw attention to the development of macular edema after cataract extraction [26]. Three years later Irvine published his classical paper on cystoid macular edema after intra- and extracapsular cataract extraction. The pathogenetic mechanism was seen in the incarceration of the vitreous at the level of the incision in the anterior segment with consecutive tugging of the vitreous on the macula [27]. A decade later, the phenomenon of cystic fluid accumulation in the macula after cataract extraction was finally demonstrated by Gass and Norton using fluorescein angiography. Fluorescein angiography added a long needed tool to the intrumentarium of retinal

specialists to detect macular edema before it is clinically evident, but also to follow-up the natural evolution or to ascertain a positive response to treatment [28].

The discovery of the blood-retinal barrier

The ensuing years brought about the characterisation of the blood-retinal barrier and its paramount role in the development of macular edema. Already in 1913, Schnaudigel described the existence of a barrier that protected the retina from the entry of the trypanblue dye which had been injected intravenously [29]. Further investigation of this barrier by Ashton led much later to the establishment of the concept of the inner and outer blood-retinal barrier and their modulation by different agents [30].

As can be seen in the first few papers of the following collection the mechanisms of this barrier are still not completely understood. But it will become clear to the reader that the underlying mechanisms of macular edema all reside within either the retinal capillary endothelium or the retinal pigment epithelium. The elucidation of these mechanisms and the possible therapeutic consequences will be the challenge of the 21st century.

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Cellular mechanisms of blood-retinal barrier dysfunction in macular edema

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Abstract. *Purpose:* To determine the mechanism of blood-retinal barrier (BRB) dysfunction in human and experimental specimens using immunocytochemistry. *Methods:* Extravascular albumin was localized in clinical specimens and retinas from transgenic mice that overexpress vascular endothelial growth factor (VEGF) in the photoreceptors. Transgenic mouse retinas were also labeled with Griffonia simplicifolia isolectin-B4 (GSA), a lectin that binds to endothelial cells. *Results:* The BRB is established by the presence of tight junctions between the retinal vascular endothelial (RVE) cells and the RPE cells and by a paucity of intraendothelial cell vesicles. When BRB breakdown occurs in human ocular disorders such as diabetic retinopathy, retinitis pigmentosa, or cystoid macular edema, staining for extravascular albumin reveals leakage through the tight junctions, an upregulation of intraendothelial vesicles, and permeation of RVE or RPE cells that have undergone degenerative changes. VEGF, in addition to inducing neovascularization (NV), promotes vascular leakage. In VEGF transgenic mice, BRB failure is confined to the outer retina, the area where NV occurs. GSA binds to the luminal and abluminal surfaces of RVE cells in new and established vessels and to intraendothelial vesicles and interendothelial cell junctions in areas of vascular leakage. *Conclusion:* BRB dysfunction may be mediated by leakage through the tight junctions of RVE or RPE cells, by trans-endothelial vesicular transport, or by permeation of RVE or RPE cells that have undergone degenerative changes. GSA may be a useful marker to assist in recognizing open tight junctions and an increase in intraendothelial cell vesicles, which are indicative of BRB failure.

Key words: blood-retinal barrier, macular edema, vascular endothelial growth factor, Griffonia simplicifolia isolectin-B4, neovascularization

Blood-retinal barrier function and dysfunction

Macular edema, resulting from a breakdown of the BRB, is the major cause of moderate visual loss in diabetics and of poor visual acquity following cataract surgery. It also leads to visual deficits in a number of other ocular disorders. Major causes of macular edema include diabetes, vein occlusions, post-intraocular surgery, uveitis, and retinitis pigmentosa; however, the cellular mechanisms by which macular edema occurs in these and other ocular disorders are not clearly understood [1–3].

The BRB consists of an inner and an outer component. The inner BRB is formed by the RVE and is established by complex tight junctions that form between the vascular endothelial cells and a paucity of intraendothelial cell vesicles. The establishment and maintenance of the inner BRB is controlled by the perivascular astrocytes. Pericytes also influence the inner BRB, but their role is less clear; however, pericyte loss, which occurs in diabetic retinopathy, leads to BRB failure. The outer BRB is established by tight junctions between RPE cells that prevent fluids from the choroidal vessels from entering the retina and by an asymmetrical distribution of proteins that regulate vectorial transport across the RPE [2, 4, 5].

The integrity of the BRB can be assessed by a variety of methods, each of which has its distinct advantages and limitations [4]. The choice of methods depends on whether quantitative or qualitative data is desired and on the nature of the tissue that is being evaluated, whether it be fixed tissue, patients in a clinical setting, or experimental animal models. Tracer molecules provide different levels of sensitivity depending on their molecular weight and charge. Vitreous fluorophotometry or the use of radiolabelled tracer molecules can be used to quantitate the extent of BRB breakdown in human or experimental subjects. Fluorescein angiography, Evans Blue Dye, and magnetic resonance imaging are useful for gross visualization of areas of leakage and magnetic resonance imaging can also provide quantitative data. Infusion of the tracers, lanthanum or peroxidase, or immunolocalization of extravasated serum proteins can be used at the light or electron microscopic level to determine sites of BRB compromise at a higher resolution and provide insights into its mechanisms from a morphological perspective; however, this cannot be performed clinically or on live animals, since fixed tissue is required. Complementary data obtained from different methods may yield a more complete picture of BRB breakdown [6].

Several limitations are associated with the use of tracer substances to assess BRB breakdown. The use of tracers is impractical for clinical studies, the introduction of exogenous material may alter BRB integrity, and retrospective studies cannot be done on archival tissues. The immunolocalization of endogenous extravascular albumin can circumvent most of these limitations and offers the following advantages for BRB assessment studies. The technique can be used with fixed surgical, autopsy, or archival specimens, no exogenous substance is introduced, and it can be used at the light and electron microscopic levels. Since albumin is confined within the vessels in the retina and other tissues with a blood-tissue barrier, the immunohistochemical demonstration of extravascular albumin is a useful tool for determining the site and extent of BRB breakdown. The location and intensity of positivity generally correlates with the location and severity of pathological findings, but in many cases BRB failure can be detected prior to any pathological

changes. The technique is applicable to a wide variety of pathologic processes and electron microscopic immunolocalization of albumin provides insights into the mechanism of BRB breakdown.

The immunohistochemical demonstration of extravascular albumin has been used to assess the BRB in a variety of ocular disorders such as diabetic retinopathy, retinitis pigmentosa, vascular occlusive disease, neoplastic disease, ocular inflammation or infection, and other disorders that develop macular edema, but for which pathological defects do not reveal a cause for BRB failure [7–12]. This technique has also been applied to experimental diabetes [13], galactosemia [14], and experimental autoimmune uveoretinitis [15]. These studies have revealed that for disorders primarily affecting the RPE, such as macular edema that results following chronic retinal detachment, BRB breakdown involves predominantly the outer BRB, but in most other cases, the inner BRB is compromised initially and the outer BRB subsequently breaks down as the disease progresses. Electron microscopic immunocytochemical staining for albumin reveals that BRB breakdown can occur by the opening of tight junctions between RVE or RPE cells, by an upregulation of trans-endothelial vesicular transport, or by increased surface membrane permeability of RVE or RPE cells resulting from degenerative changes associated with the disease process [13, 15–17].

Based on the electron microscopic immunolocalization of albumin, some functional opening of RVE tight junctions appears to occur in diabetic rabbits, but little or no opening of RVE tight junctions is seen in diabetic humans or rats or in galactosemic rats [6]. Rather, the principal mechanisms for BRB breakdown in diabetes appear to be an upregulation of trans-endothelial vesicular transport and increased membrane permeability that results following degenerative changes that occur to the RVE and RPE cells as the disease progresses [13, 14, 17, 18]. Many ocular disorders such as ocular melanoma, demonstrate widespread BRB breakdown in areas far removed from the structural defect, suggesting that the BRB failure is mediated by soluble factors. A number of candidates, which are known to facilitate BRB breakdown, include adenosine, prostaglandin E_1 (PGE_1), tumor necrosis factor α (TNFα), interleukin-1ß (IL-1ß), and VEGF [10, 15, 16, 19–28].

Adenosine is postulated to promote macular edema in ischemic retinopathies [29] and prostaglandins are likely to play a role in aphakic macular edema [30, 31]. TNFα [32, 33], IL-1ß [33], and VEGF [34, 35] are upregulated under ischemic conditions and IL-1ß gene expression is induced in retinal glia, retinal vascular endothelial cells, and neutrophils recruited into the retina during reperfusion after retinal ischemia [36]. These mediators are likely to play a significant role in the development of macular edema in ischemic retinopathies, ocular inflammatory disease, and other ocular disorders.

When administered intravitreally, each of these mediators appears to be capable of causing a morphological and functional opening of the RVE tight junctions and an upregulation in vesical-mediated transport across the RVE [15, 16, 28, 37, 38]. A significant number of interendothelial cell tight junctions appeared open along their entire length within 6 hours after intravitreal injection of each agent into rabbits with TNFα showing the greatest effect (35.6% of the interendothelial cell junctions appeared morphologically open) and VEGF, the adenosine agonist N-ethylcarboxamidoadenosine (NECA), PGE_1, and IL-1ß also showing substantial increases [15, 16]. The effect of PGE_1 on tight junctions appeared to be reversible, that of VEGF and IL-1ß were partially reversible by 24 h, and the effect of NECA was not reversible after 48 h. The demonstration of immunoreactive albumin along the entire length of these junctions, from the luminal to the abluminal surface, suggests that they are also functionally open. Intravitreal treatment with each of these agents also leads to the formation of pinocytotic vesicles in the RVE cells and the distribution of albumin-containing intraendothelial vesicles across the entire RVE cell and at both the luminal and abluminal surfaces suggests that active vesicular transport is occurring. Although infrequently seen, the vesiculo-vacuolar organelle [39], which is associated with VEGF in the vascular endothelium of tumors, was also evident in the RVE of VEGF-treated rabbits and is likely to play a role in VEGF-mediated vascular permeability. The effect of these factors on the outer BRB is less clear, but it is highly likely that soluble mediators play a major role in BRB breakdown in human ocular disease.

The capability of VEGF to induce neovascularization has been well documented in different species. When slow release pellets composed of ethylene-vinyl acetate copolymer containing VEGF were implanted into the vitreous of rabbits, prominent retinal NV resulted within two weeks [28]. Many of the nuclei of the vascular endothelial cells stained for proliferating cell nuclear antigen (PCNA), indicating that the RVE cells were actively proliferating. Similar pellets implanted into the vitreous of monkeys induced marked vascular dilation of the inner retinal vessels, but PCNA staining did not substantiate NV, although electron microscopy suggested it may have occurred [28]. Immunohistochemical staining for albumin revealed that these grossly dilated vessels were leaky.

There is evidence that VEGF contributes to BRB breakdown, leading to macular edema in human ocular disease. Normal human retina contains little or no VEGF, but it is induced by hypoxia and it is upregulated in ischemic retinopathies, such as diabetic retinopathy, vascular occlusive disease, and retinopathy of prematurity. VEGF is, however, also upregulated in a variety of ocular disorders that lead to macular edema, but do not present with pathological evidence of ischemia, including ocular inflammation, ocular infec-

tions, aphakic or pseudophakic cystoid macular edema, retinoblastoma, and choroidal melanoma [12]. In addition, a marked increase in VEGF is demonstrated in the inner retina of rats and mice developing experimental autoimmune uveoretinitis (EAU) resulting from immunization to the photoreceptor-specific S-antigen [28, 40]. VEGF can be localized in retinal vessels, ganglion cells, retinal glia, RPE cells, and photoreceptors. VEGF immunoreactivity frequently co-localized with sites of increased vascular permeability [12, 21, 27], but in other cases, it had a widespread distribution throughout the retina. Despite marked upregulation of VEGF in the retina in EAU and a variety of non-ischemic retinal disorders, NV often does not occur. This may be due to the presence of an endothelial growth inhibitor, such as TGF_{β} [40], or to a deficiency of receptors. VEGF may still function in these examples as a permeability factor and in autoimmune disease and ocular infections, it may play a role in mediating an immune response as has been suggested by previous reports showing that VEGF can promote the activation and migration of monocytes [41] and that both VEGF [42] and TNFα [43] can promote adhesion of activated natural killer cells to vascular endothelium through ICAM-1 and VCAM-1. In addition, VEGF is upregulated immediately prior to lymphocyte infiltration in EAU [12] and experimental herpesvirus retinopathy [44], further supporting the hypothesis.

Many of the effects of VEGF can be mediated by other factors and the events that induce VEGF can initiate a cascade of factors. It is often unclear what the initial event is in this cascade. To more clearly understand the role of VEGF in the retina, a transgenic line of mice was generated in which the VEGF gene is coupled to the rhodopsin promoter, leading to an overexpression of VEGF by the photoreceptors [45]. In these mice, VEGF transgene mRNA was first detected in the retina by reverse transcriptase polymerase chain reaction (RT-PCR) on postnatal day 6 [46]. The VEGF mRNA level increases until the fourteenth postnatal day and remains constant for the next week. Retinal NV occurred in the transgenic mice and using fluorescein angiography with confocal microscopy and electron microscopy, it appeared that the NV originated only from the deep capillary bed, beginning at 10-14 days postnatally, with the superficial retinal vessels and the choroidal vessels unaffected. Image analysis revealed that the newly-formed vascular complexes gradually enlarged and coalesced and the subretinal NV was progressively engulfed by the RPE.

Griffonia (Bandeiraea) simplicifolia isolectin B_4(GSA) is a lectin that can be used to effectively label murine endothelial cells [47]. The following method was applied to label the transgenic mouse eyes with GSA to visualize the neovascular events. The corneas were removed from normal (PCR-negative), and VEGF-transgenic mouse eyes and the eyes were fixed in a solution of 4% paraformaldehyde and 0.2% glutaraldehyde containing 8.5%

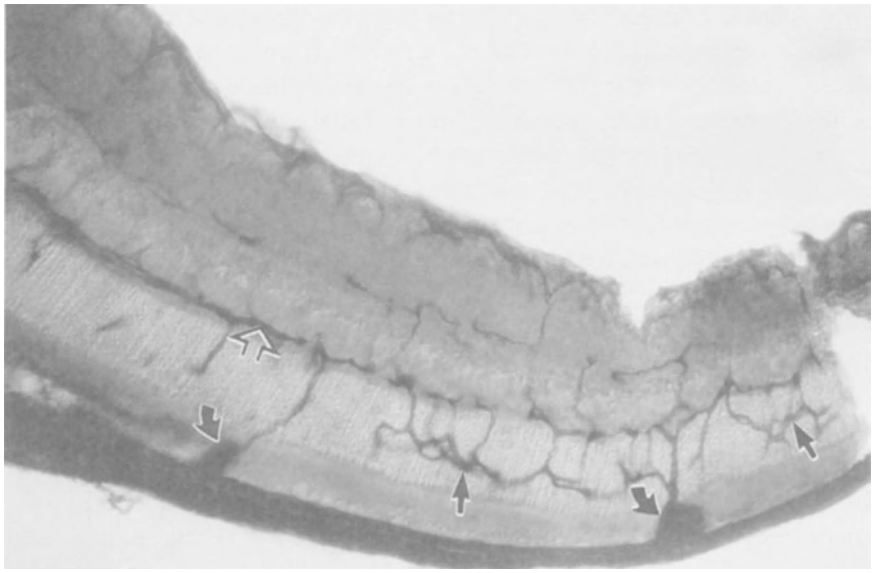

Figure 1. A GSA-labelled vibratome section from an 18-day postnatal VEGF-transgenic mouse retina showing NV. Normally, vessels do not extend external to the deep capillary bed in the outer plexiform layer (open arrow), but numerous newly formed vessels can be seen extending through the outer nuclear layer to Bruch's membrane (bottom). Note interconnecting vessels in outer nuclear layer (straight, solid arrows) and vascular complexes (curved arrows) adjacent to Bruch's membrane.

sucrose and 1 mM $CaCl_2$ in 0.1 M bicarbonate buffer, pH 10.4, and incubated overnight at 4 °C. The eyes were placed in phosphate-buffered saline, pH 7.4, containing 1 mM $CaCl_2$ and 50 μm sections were cut on a vibratome (Lancer series 1000). The sections were infiltrated with Poly/Bed 812 (Polysciences; Warrington, PA) and placed between slides that had previously been coated with dimethyldichlorosilane, as previously described [48]. After polymerization at 60 °C, the resin can be peeled from the slides and the sections viewed and photographed by light microscopy and optimal areas can be subsequently re-embedded for electron microscopy. These preparations clearly confirmed that the NV originated entirely from the deep capillary bed. In mice in which NV had not occurred, the large inner retinal vessels, the vessels of the superficial and deep capillary beds with some vessels shunting both beds, and the optic nerve vessels were clearly visualized, but there was no staining in the outer nuclear layer or among the outer segments of the photoreceptors. GSA clearly demonstrated vascular sprouts originating from the vessels in the outer plexiform layer and initially extending as delicate outgrowths into the outer nuclear layer. These newly formed vessels extended through the photoreceptor layer and formed large vascular complexes at the level of the

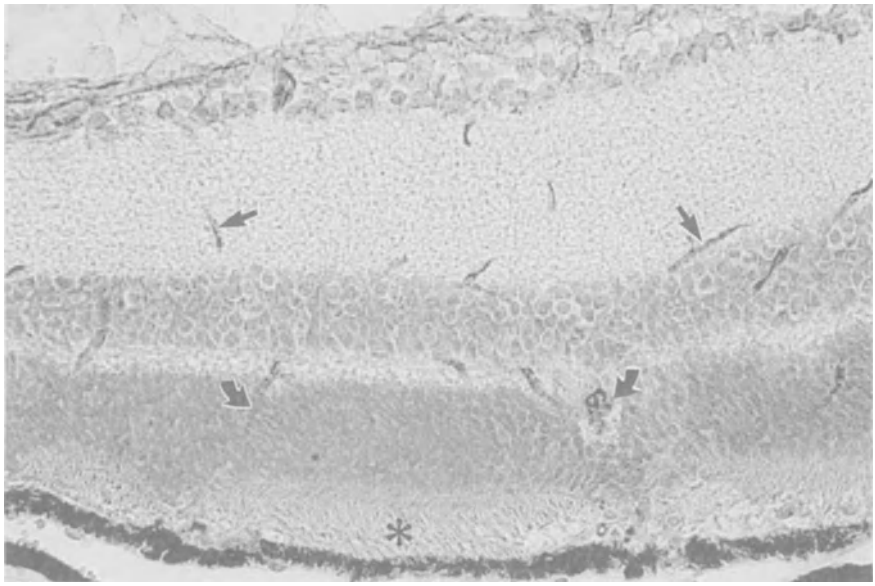

Figure 2. Immunohistochemical staining for albumin in the retina of a VEGF-transgenic mouse with retinal NV. All retinal vessels are positive (straight arrows), but extravascular albumin is demonstrated only in the outer retina (asterisk), the area where NV is occurring. Note darker coloration in the outer retina due to reaction product than in inner retina and note NV extending into outer nuclear layer (curved arrows).

RPE (Figure 1). It is not clear whether the vessels in the superficial capillary bed and the choroid are unresponsive to the VEGF generated by the transgene or if the VEGF is inaccessible to these vessels due to physical constraints (for example, the tight junctions of the RPE and the inability to diffuse through several layers of the retina). Immunohistochemical staining for albumin shows that BRB breakdown occurs only in the area of NV (the outer retina) (Figure 2).

GSA binding can also be visualized at the ultrastructural level. It reveals vascular sprouts emanating from vessels in the outer plexiform layer in the early stages of NV and gradually extending through the outer nuclear layer and towards the RPE. Initially these sprouts consist of clusters of cells without a lumen and, without the GSA labelling, they would be very difficult to recognize as endothelial cells. Lumens eventually form and red blood cells can be seen within the lumens. No differences were noted when comparing inner retinal vessels of normal and transgenic mice.

In addition to decorating the luminal and abluminal surfaces of nearly all vascular endothelial cells from normal retinal vessels and those in neovascular areas, most pericytes and perivascular basement membranes showed

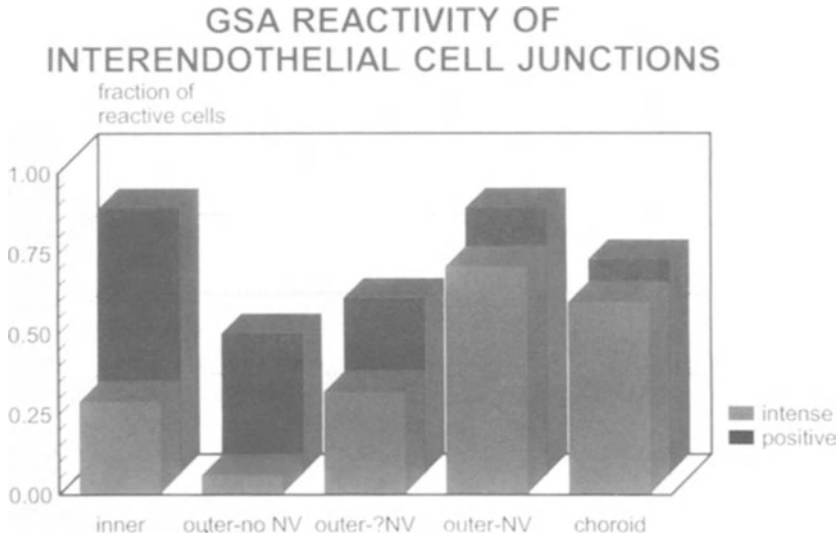

Figure 3. The fraction of interendothelial cell junctions between retinal vascular endothelial cells reacting positively with GSA or staining intensely is graphed to compare inner retinal vessels (inner), outer retinal vessels in areas with no neovascularization (outer-no NV) or possible neovascularization (outer-? NV), neovascularization in the outer retina (outer-NV), and choroidal vessels (choroid).

at least some GSA binding. Labelling at these sites did not show consistent differences between new and established vessels, but a considerable increase in the number of interendothelial cell junctions that bound GSA was noted in newly-formed vessels when compared to established vessels (Figure 3). The number of labelled junctions in areas of NV was comparable to the interendothelial cell labelling seen in choroidal vessels and corresponded to the vascular leakage that was apparent in these areas. It is likely that GSA may only be able to access its interendothelial cell binding sites when the cell junctions are 'open'. In addition, GSA labelled intraendothelial cell vesicles in areas of NV and may be useful in recognizing areas where trans-endothelial vesicular transport is active as a mechanism of BRB compromise (Figure 4).

Conclusions

There are three cellular mechanisms of BRB breakdown: (1) leakage through the 'tight junctions' of the RVE or the RPE, (2) upregulation of vesicular transport, or (3) permeation of the surface membranes of the RVE or the RPE. BRB dysfunction may occur as a result of structural defects or follow-

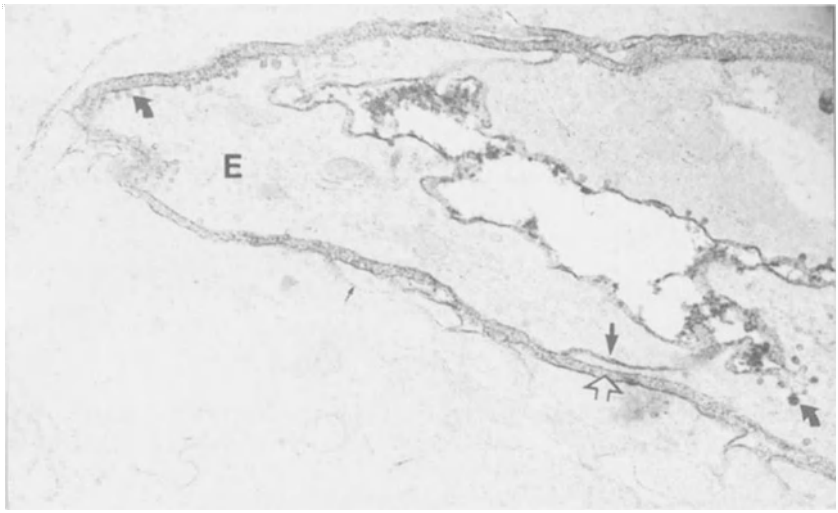

Figure 4. Electron microscopic localization of GSA-binding sites in a vessel from the outer plexiform layer of a 14-day old VEGF-transgenic mouse undergoing neovascularization. Note labelling of both the luminal and abluminal surfaces of the vascular endothelial cells (E), some pericyte membranes (small, straight arrow), perivascular basement membranes (open arrow), interendothelial cell junctions (larger, straight arrow), and intraendothelial cell vesicles (curved arrows) along the luminal and abluminal surfaces and within the cytoplasm.

ing exposure to a soluble mediator. In the murine model of NV induced by overexpression of VEGF, BRB breakdown is confined to areas of NV in the outer retina. GSA binds to the luminal and abluminal surfaces of nearly all RVE cells and to many pericytes and perivascular basement membranes. GSA labels vascular sprouts prior to the formation of discrete vessels, including clusters of cells that would otherwise be difficult to recognize as vascular endothelial cells. GSA labels interendothelial cell junctions and intraendothelial cell vesicles coincident with BRB breakdown and may be a useful marker for recognizing sites of BRB compromise.

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The molecular structure and function of the inner blood-retinal barrier

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Key words: tight junctions, ZO-1; occludin, VEGF, blood-retinal barrier

Introduction

The integrity of the inner blood-retinal barrier (BRB) has long been recognized as an important component of normal visual function, and disruption of the BRB characterizes many retinal disorders. Macular edema in particular results from water, albumin and lipid leakage, with accumulation of lipid exudates and intraretinal fluid. This chapter will review BRB structure-functional relationships, highlight recent observations regarding molecular physiology of the BRB, and discuss how these concepts may be applied to the diagnosis and treatment of retinal vascular disorders, such as macular edema.

The concept of the inner BRB was first developed three decades ago based on the similarity to the blood-brain barrier (BBB) [1]. Like the BBB, the BRB is composed of tight junctions between endothelial cells of the retinal vascular tree. As pointed out by Alan Bird, this 'barrier' serves as a selective partition between the retina and the circulation, and to maintain the highly specialized environment of the neural tight junctions. It should be emphasized that the BRB is not an absolute obstacle to exchange of molecules from the circulation into the retina or *vice versa*. Rather, it provides a selective mechanism so that the retina can regulate its environment in response to varying metabolic demands. In particular, the retina must be able to regulate its osmotic balance, ionic concentration, and nutrients, including sugars, lipids, and amino acids, and must exclude immunoglobulins and circulating immune cells. In addition the retina must uniquely maintain its transparent

properties for normal visual function. The retina, like the brain, has adapted selective mechanisms for amino acid and glucose uptake. For example, the amino acid, glutamate, is present in plasma at approximately 100 fold excess compared to the extracellular space of the retina. Glutamate is an essential neurotransmitter for inner retinal neurons, and excessive glutamate may be toxic to neurons. Although glutamate uptake is not regulated the uptake of leucine, a glutamate precursor, is regulated. Thus, understanding the cellular and molecular factors which underlie the structure of the BRB is important for understanding the pathogenesis of macular edema.

Cellular factors involved in BRB development

The retinal vessels lie within a network ('retina') of neurons and glial cells. Neurons and glia provide signals which cause vessels to behave differently in the retina than in peripheral tissues, such as skin or gut. Several lines of evidence suggest that glial cells (astrocytes and Müller cells) play this role in the retina as astrocytes do in the brain. First, astrocytes induce central nervous system barrier properties in non-CNS vessels in transplantation studies [2]. Secondly, astrocytes guide the migration of retinal blood vessels peripherally from the optic disc through the retina during fetal life [3]. Third, brain astrocytes increase barrier properties in retinal endothelial cells from a different species; e.g. rat brain astrocytes influence bovine retinal endothelial cells [4, 5]. These observations suggest a highly conserved interaction between astrocytes and endothelial cells. These effects are mediated by soluble factor(s) which are likely to be peptides.

In addition to inductive effects of astrocytes on the BRB, the geographic distribution of astrocytes in the mammalian retina is particularly notable. The highest density of astrocyte investment of retinal vessels is around the optic disc, and the lowest is around the fovea [3]. In fact, Müller cells are absent from the central macula and only a few astrocytes are present at the edge of the fovea (Figure 1). Since astrocytes induce barrier properties the relative lack of astrocytes in this region is a potential anatomic explanation for the development of edema in the macula compared to other regions of the retina.

Molecular structure of the BRB

The molecular architecture of tight junctions has been increasingly recognized over the last decade. At present, at least eight proteins have been identified in the peripheral cytoplasm and plasma membrane of endothelial and epithelial cells. These proteins function as a complex to regulate paracellular permeability [6] (Figure 2). Of these, occludin is a 65kDa protein which spans the plasma membrane with four transmembrane domains. At its carboxy-

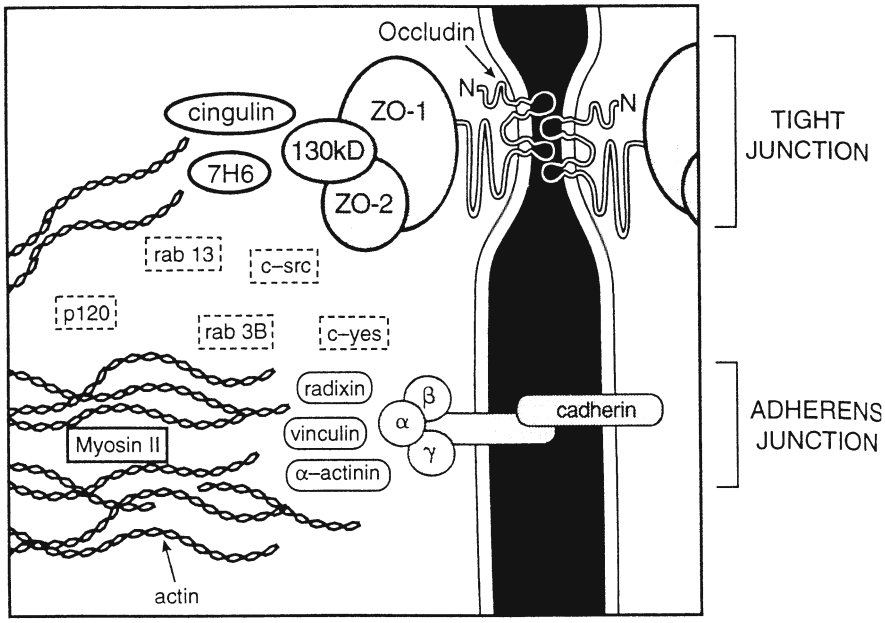

Figure 1. Schematic representation of proteins associated with tight junctions. p130 is now called ZO-3. (from Ref. 6).

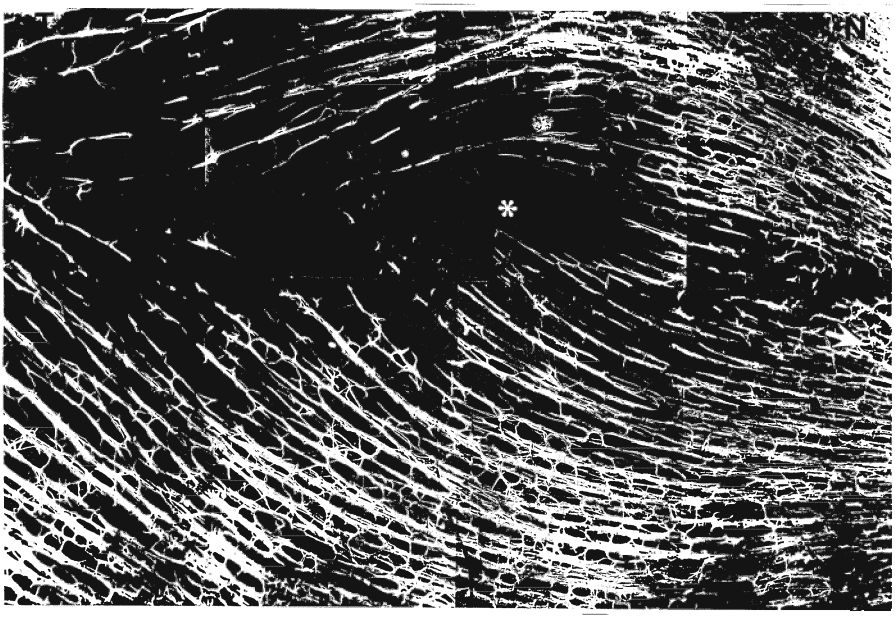

Figure 2. Distribution of astrocytes around the fovea in monkey eye. Note the astrocytes decrease near the fovea. (from Ref. 3).

Schematic of Tight Junction Alteration in Response to Vasoactive Stimuli

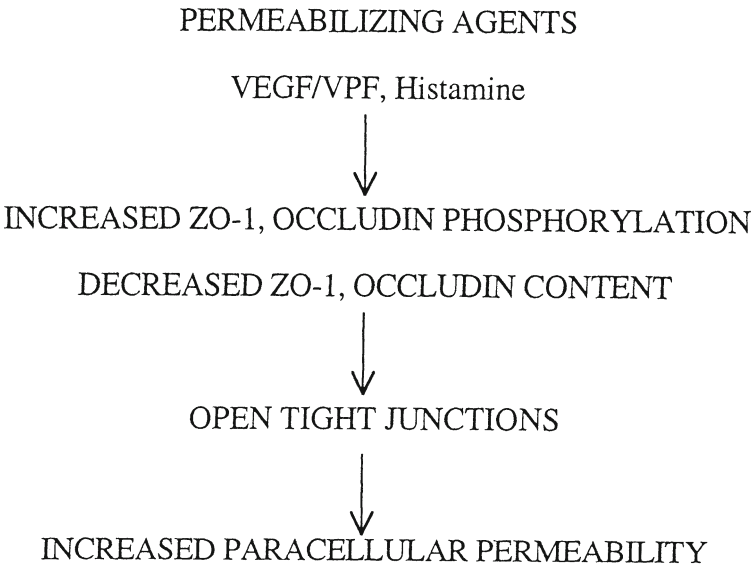

Figure 3.

terminal end it binds ZO-1, a 225 kDa phosphoprotein. In addition, ZO-2, ZO-3, symplekin and claudins have also been identified and characterized. ZO-3 binds to ZO-1 and occludin [7]. Cingulin and the 7H6 antigen are also associated with the tight junction complex but have not yet been characterized biochemically. This assembly of proteins lies at the peripheral cytoskeleton and may associate with actin filaments which undergo rearrangement when permeability increases. In addition several signalling molecules, including small G proteins, rab13 and a large G protein are present in the region of tight junctions. At present it is not clear how tight junction proteins interact or how they physically influence the paracellular flow of molecules. Nevertheless, it is clear that these proteins change in response to conditions which alter vascular permeability.

In keeping with the observations that astrocytes influence permeability of brain capillary endothelium, we showed that astrocytes increase barrier

properties (transendothelial electrical resistance) and increase ZO-1 content in cultures of bovine retinal endothelial cells. This effect is heat-labile, is mediated by soluble factors, and does not require cell-to-cell contact [5].

Conversely, factors which increase vascular permeability, notably histamine, reduce tight junction protein expression in a time course and concentration-dependent fashion that parallels clinical increases in tissue edema; i.e. within 1 hour of exposure. The histamine effect on ZO-1 content is mediated by both H_1 and H_2 receptor subtypes [8]. Although histamine reduced ZO-1, it did not change GLUT1 content. GLUT1 is generally thought to be a marker for cellular polarity and is a plasma membrane associated protein. Thus, these findings suggest that vasoactive factors may selectively alter tight junction proteins without changing the overall polarity of differentiated endothelial cells. In fact, if cells are to respond to varying influences to regulate their paracellular permeability, one would expect that they would be able to maintain their polarity and differentiation.

The physical means by which tight junctions maintain a regulated barrier remains unknown. However, the relationship between the tight junction-associated proteins and regulation of permeability is well established. For example, ZO-1 is expressed in all endothelial cells, is a component of the BRB and BBB, and its expression increases with barrier tightness. Furthermore, factors which increase permeability simultaneously decrease ZO-1 protein content. Most likely, ZO-1 serves as an organizer of tight junction complexes. The existing data suggest that occludin content most closely correlates with barrier properties. Endothelial cells of non-neural tissue express less occludin, where it is distributed in a discontinuous fashion at cell-to-cell contacts [9]. Reduction of occludin by anti-sense oligonucleotides increases permeability [10]. Thus, occludin likely regulates barrier function.

One of the most important questions is whether tight junction proteins change in disease conditions and contribute to BRB permeability *in vivo*. We have found that experimental diabetes in rats significantly reduces occludin content contemporaneous with increased BRB permeability to albumin [11]. In addition, vascular endothelial growth factor/vascular permeability factor (VEGF/VPF) significantly reduces occludin content in retinal endothelial cell cultures and rapidly increases hydraulic conductivity (water permeability) across endothelial cell monolayers [12]. Together these findings suggest that tight junction protein content is an important regulator of paracellular permeability. Prior studies of the BRB in diabetes have emphasized morphologic changes in tight junctions with transmission electron microscopy [13–14]. These studies found no intercellular accumulation of native albumin. Of note, in these studies the diabetic rats were pretreated with the histamine H_1 receptor antagonist, diphenhydramine. Since BRB permeability in rats is par-

tially mediated by histamine receptors and blocked by histamine receptor antagonists [15], the use of diphenhydramine may have confounded the results. In keeping with the reduction of tight junction proteins by VEGF, a recent report showed that intravitreal VEGF/VPF in normal rabbit eyes maximally opened tight junctions (as determined by electron microscopy) at 6 hours with partial resolution by 24 hours [16]. This time course is consistent with our findings. While formation of transcellular channels or vesicle movement may also contribute to increased vascular permeability in diabetes, the above morphological changes in tight junctions provide strong evidence for their role in increased paracellular flux in response to VEGF/VPF.

In addition to regulating protein content, there is also evidence that tight junction protein phosphorylation is altered in conditions associated with increased permeability. ZO-1 tyrosine phosphorylation induced by epidermal growth factor (EGF) was first associated with increased glomerular permeability in kidneys [17]. By using the calcium-switch model in which depletion of extracellular Ca^{++} increases permeability, Furuse et al. [18] have shown a shift in relative mobility of occludin on SDS-PAGE and suggested that changes in occluin phosphorylation may be associated with organization of tight junctions. We demonstrated recently that the potent permeabilizing agent, VEGF/VPF, rapidly increases the phosphorylation state of occludin coincident with increased permeability. This change in phosphorylation state is distinct from that observed by Furuse in the relative mobility of occludin on SDS-PAGE gels. Tyrosine phosphorylation of ZO-1 also occurs in a transient manner following VEGF/VPF exposure [19]. The phosphorylation response is more rapid than the protein content changes, and both are spontaneously reversible. These data suggest a model whereby endothelial cells can intricately regulate paracellular permeability in response to external vasoactive ligands, and more prolonged stimulation may induce tight junction protein degradation. At this point it is unknown whether or not there is a connection between phosphorylation and reduction of protein content. Overall, molecular analysis of tight junction proteins allows for detection of subtle alterations in tight junction composition and function which are not detectable by morphologic evaluation alone.

Tight junction proteins and macular edema

The production of tissue edema requires that the movement of fluids and solutes from the intravascular to the extravascular space be greater than the removal of fluids in the opposite direction. This may occur with increased hydrostatic pressure, such as from hypertension, or from increased tissue oncotic pressure. However, breakdown of the BRB will change the equilibrium between the intervascular and extravascular spaces. How then, could

alterations in tight junction protein composition contribute to the production of macular edema? A schematic diagram is presented in Figure 3. According to this hypothesis, vasoactive factors such as VEGF/VPF, histamine or other factors may act directly on the endothelial cell tight junctions to decrease their protein content or increase their phosphorylation. Either or both of these effects may increase paracellular permeability. The specific molecules which are allowed to move through intercellular junctions may depend on the specific vasoactive factor, its concentration, duration of action, or interaction with other factors. For example, in cystoid macular edema both water and proteins accumulate within the cyst, but inflammatory cells and erythrocytes usually do not. This would suggest that the tight junctions can selectively regulate molecules which pass through intercellular junctions. This selectivity may not be related strictly to molecular mass, but could also be related to hydrophobicity or electrical charge. The relative paucity of astrocytes around the fovea may provide less tonic control of tight junctions and may increase the propensity for BRB breakdown in this area in response to inflammatory states such as uveitis or aphakia.

In summary, understanding the regulation of tight junction proteins by phosphorylation and protein content may lead to improved means to control BRB function and to treat macular edema and other retinal vascular disorders, including diabetic retinopathy. For example, corticosteroids increase tight junction protein expression in retinal endothelial cells [20], and this observation may help to explain the beneficial effect of steroids on macular edema. Further knowledge of the molecular mechanism which underlies this response may lead to development of more specific and effective therapy.

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Mechanisms of fluid accumulation in retinal edema

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Abstract. This paper reviews the anatomic and physiologic conditions which predispose to fluid accumulation within the retina. Retinal edema has its inception in disease that causes a breakdown of the blood-retinal barrier in retinal capillaries and/or the retinal pigment epithelium (RPE). Edema develops not only because protein and fluid enter the extracellular space, but because the external limiting membrane and the convoluted extracellular pathway within the retina limit the clearance of albumin and other large osmotically-active molecules. These molecules bind water to cause edema. Recognition of edema clinically is complicated by the facts that angiographic markers (fluorescein and ICG) do not match albumin in size, and that clinical leakage does not always correlate closely with tissue swelling or functional loss. Active water transport across the RPE is efficient at removing subretinal water, but the flow resistance of the retina limits RPE access to the water of retinal edema. Consideration of the pathophysiology of retinal edema may aid in the development of better strategies for managing retinal edema.

Key words: blood-retinal barrier, external limiting membrane, macular edema, retinal pigment epithelium

Abbreviations: BRB – blood-retinal barrier; CSC – central serous chorioretinopathy; ELM – external limiting membrane; ILM – internal limiting membrane; RPE – retinal pigment epithelium; SRS – subretinal space

Introduction

The retina is an outgrowth of the developing brain, and as such its neural constituents require the same protection as brain tissue from unwanted extracellular fluid. Free leakage of fluid and protein from the vasculature is prevented by the blood-brain barrier, which in the retina is formed by tight junctions between the endothelial cells of the retinal capillaries and between the cells of the retinal pigment epithelium (RPE). Thus, the interstitial spaces of the retina are normally quite dry. There may be a slow percolation of water into the retina from intraocular pressure, but without solutes it is not retained and active transport across the RPE removes this water as fast as it gets through.

In a variety of diseases, the blood-retinal barrier (BRB) is disrupted so that water accumulates in the retina and causes the tissue to thicken with edema. Depending on the cause, severity and duration of edema in the mac-

ula, vision may be decreased. Despite the clinical prevalence of macular edema in diseases such as diabetes, retinal vein occlusion, uveitis, retinitis pigmentosa and post-cataract surgery, the mechanisms that lead to edema are incompletely understood. Edema is not necessarily or simply a result of water and protein leakage, and the relationship of edema to visual function can be complicated. The most common imaging technique, fluorescein angiography, technically shows neither the movement of water nor protein – and of course it cannot assess cellular damage or cellular swelling that may be present in some edema-causing diseases.

This brief review will offer a framework for thinking about retinal edema and for weighing the various contributory factors. I will assume for this discussion that the main sources of edema fluid are the retinal and choroidal vasculatures, and that opening the blood-retinal barrier at either the level of retinal capillaries or the RPE is a clinically relevant event. We still must consider how the specialized structures of the retina, and the available fluid absorptive forces, favor edema under conditions of disease.

Anatomic considerations and protein movement

Although the primary blood-retinal barrier is formed by the tight junctions (zonula occludentes) of the retinal capillary endothelial cells and the RPE, other structural features of the retina serve as relative barriers to water and protein movement that are relevant to the formation of edema. Retinal tissue as a whole impedes the free flow of water [1] to a degree that limits the rate at which water leaves the eye across the RPE. The normal RPE is capable of pumping a lot more water per minute than leaves under normal conditions [2], because water cannot pass through the retina any faster. There are no anatomic barriers to water movement in the retina (i.e., tight junctions) but the interstitial pathway from vitreous to subretinal space (SRS) is long and convoluted, and it ends with a band of zonula adherens that form the external limiting membrane (ELM). The internal limiting membrane (ILM) consists only of matrix material and some condensed vitreous collagen, and is probably not a significant impediment to water or solute movement [3]. However, the zonula adherens between the Müller cells and photoreceptors at the base of the outer segments, which make up the ELM, have only a very narrow channel [3]. They are not sealed like the zonular occludens of the RPE and retinal capillaries, but they limit particularly the movement of large molecules. A study on the rapid passage of proteins across the ELM suggested that the effective 'pore' size of the ELM was smaller than albumin [4]. However, later work has shown definitively that albumin can pass through the ELM with only a relative degree of impediment. For example, fluores-

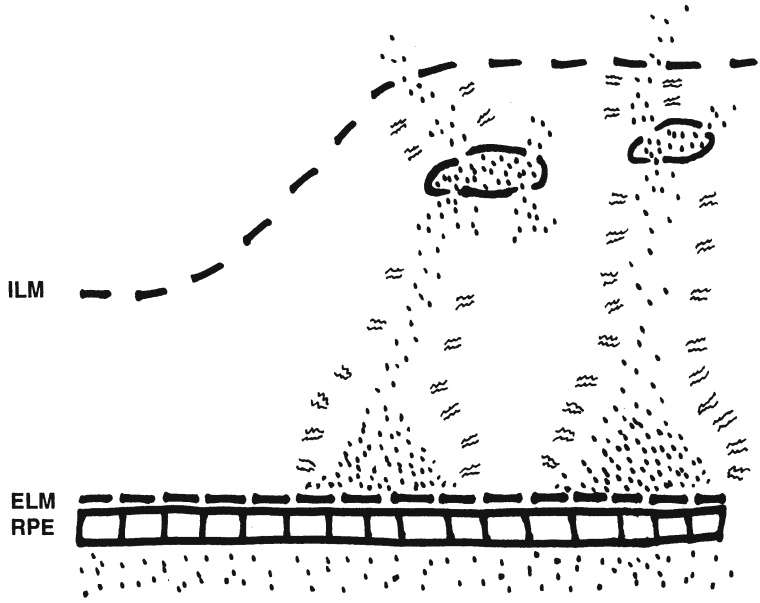

Figure 1. Diagram of leakage from damaged retinal vesels. Protein can diffuse freely towards the vitreous, but is stopped at the ELM and RPE. The intraretinal protein binds water osmotically to cause edema.

ceinated albumin leaking out of osmotically injured retinal capillaries can be seen histochemically to reach the subretinal space [5]. And in experiments where fluoresceinated albumin was injected into either the subretinal space or the vitreous [6, 7], it diffused steadily into the other compartment. The rate of albumin movement across retina is substantial, amounting to 4–5% of the concentration difference across the retina per hour.

These observations have implications for clinical edema. Large molecules do not diffuse freely across the retina, but traverse in relation to their size [8], and are blocked partially by the ELM. Thus, protein that is released within the retina will tend to remain for a period of time, and in particular will tend to back up behind the ELM which slows its movement more than the general interstitial pathways (Figure 1). To the extent that protein is retained, water will also be retained osmotically. On the other hand, to the extent that albumin does traverse the retina, clinical conditions that produce persistent edema must leak protein continually to replace that which diffuses away into the vitreous or subretinal space.

Absorptive forces for water

In a normal eye, both passive and active forces work to move water across the retina and out of the subretinal space. First, intraocular pressure is continually pushing water into the retina, although only a very small flow through occurs because of the flow resistance of the retinal tissue. Second, choroidal osmotic pressure draws water towards the choroid. These two passive forces are very strong, and in fact are quite sufficient to keep retina in place and the subretinal space dry without the intervention of active RPE transport! In surgical procedures where RPE and choroid have been removed (e.g., en bloc resection of choroidal melanoma) the retina quickly flattens and remains in place. Furthermore, when saline fluid is introduced experimentally into the subretinal space, it is absorbed *faster* if the RPE barrier is damaged than if it is intact [9, 10]. Thus passive RPE barrier damage does not by itself block fluid absorption or cause *sub*retinal fluid to accumulate. However, as will be discussed later, protein movement through a damaged barrier may play a role in the accumulation of fluid or edema *within* retinal tissue.

If passive fluid absorption is so strong, why do we need active transport across the RPE? We need it because the requirement for a protein-free neural environment dictates that there be a blood-retinal barrier on the RPE side, and the resulting tight junctions impede the passive absorption of fluid. Active transport is necessary to remove water that percolates through the retina from intraocular pressure, and perhaps also as a safety mechanism against fluid accumulation in disease. The cells of the RPE are separated into apical and basal regions by the tight junctional barrier, and contain an array of channels and transport systems that are specialized to either the apical or basal cell membranes. In other words, a number of ionic transport systems are at work simultaneously, some of which move ions in an apical direction and some of which move ions in a basal direction. These apical-to-basal differences (for example, the electrogenic Na-K exchange pump is present only in the apical membrane) result collectively in a net movement of ions in the apical-to-basal direction that carries ('pumps') water [11]. While the net balance is normally toward the removal of subretinal fluid, pathologic or therapeutic modification to these transport systems can either enhance or impede water removal, depending on the particular channels that are affected.

It is likely that almost any retinal disorder which involves metabolic dysfunction or choroidal vascular insufficiency will alter RPE transport to some degree. A diffuse diminution of RPE transport may explain why *subretinal* fluid accumulates and persists in a disease such as central serous chorioretinopathy (CSC) where there is only a small focal source of fluid entry [12, 13]. The underlying pathology in this disorder is probably an alteration of the choroidal vasculature by adrenaline and cortisol secretion in stress-prone

individuals, with secondary compromise of membrane transport across the RPE. However, while RPE transport is clearly critical to the removal of subretinal fluid, it is not always clear how relevant it is to retinal edema, since the rate of removal of *intraretinal* water may be limited by the ability of water to traverse the retina and enter the subretinal space (where the RPE will have access to it). This may be one reason that intraretinal fluid (retinal edema) seems to be more prevalent clinically than subretinal fluid.

Mechanisms of retinal edema

The term 'edema' describes swelling from fluid but does not specify where the fluid resides. Either *extra*cellular or *intra*cellular fluid may result in edema, and in fact both are likely to occur in many retinal disorders. All cells maintain internal homeostasis on the basis of membrane transport systems that balance ionic movements in and out of the cell. And many of the same pathologic insults (for example, ischemia) that open the BRB also damage membrane ionic channels and can lead to cellular swelling. Thus, neuronal and/or glial swelling may often be a component of retinal edema – probably most prominently in areas of ischemic capillary loss where there is a severe metabolic insult and no viable capillaries to generate extracellular fluid. There may also be secondary interactions between BRB damage and stromal membrane damage to the extent that an altered extracellular environment may be injurious to cell membranes, while intracellular decompensation can lead to a release of excitotoxins or free radicals that may in turn affect the BRB.

Granting that intracellular swelling plays a role in some types of macular edema, it is still important to ask how extracellular fluid can accumulate in a thin tissue such as retina with no barriers against water escaping into the vitreous. One of the answers must be protein. In diseases with a breakdown of the BRB in the retina, albumin and other proteins will be forced by blood pressure and diffusion gradients into the extracellular space of the retina where they can move slowly in all directions. At the ILM, the protein can leave the retina freely but at the ELM, protein will tend to back up within the retinal tissue (Figure 1) This accumulation of protein will create oncotic pressure, bind water and thus create a condition of retinal edema. Edema will probably be greatest near the sites of leakage (retinal capillary layers) and at the sites of protein build-up (ELM). One might ask why the protein does not also build up within the SRS and cause a serous detachment. The primary reason is that the active transport capacity of the RPE is great enough to overcome oncotic effects. In experiments where serum or fluoresceinated dextran in saline were injected into the SRS, fluid absorption still occurred vigorously

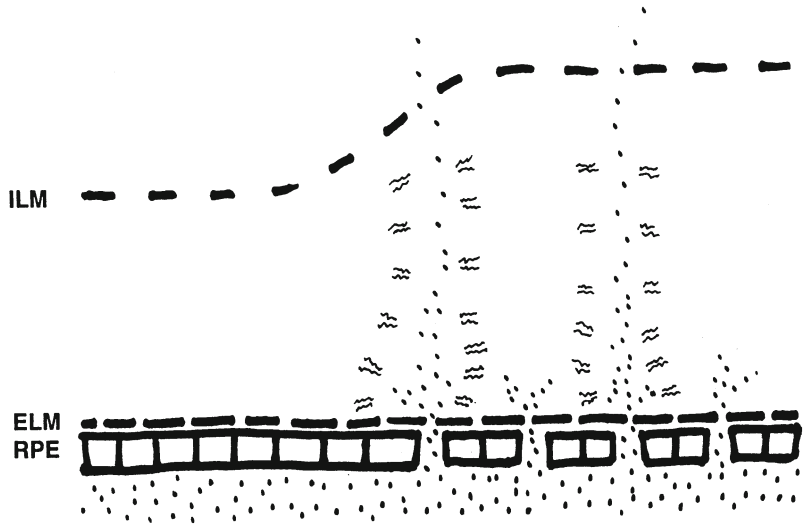

Figure 2. Diagram of leakage across damaged RPE. Although the ELM is a relative barrier to protein, some will pass through. As protein diffuses across the retina towards the vitreous it binds water and causes edema.

to the point of leaving residue in the SRS [8, 10]. This may account for the subretinal exudate seen occasionally in cases of severe retinal edema.

There is good evidence that in most diseases of the BRB, both the retinal capillaries and RPE are affected to some degree, although some cases of retinal edema seem mostly from retinal capillary leakage while others show diffuse RPE leakage with little capillary damage [14]. Why does RPE damage lead to retinal edema when proteins are not being released into the retinal substance? The answer probably derives from the fact that although the ELM inhibits the passage of protein, it does not stop it altogether. Thus, if albumin reaches the SRS, some of it will diffuse into and through retina. The concentration gradient of retinal protein will be highest at the RPE side where protein crosses the ELM, and will diminish towards the vitreous (Figure 2). Whereas the oncotic pressure of protein does not hold water within the SRS because of active RPE transport, protein that enters the retinal extracellular space can retain the osmotic complement of water. Thus, damage to the RPE barrier can lead to retinal edema from passive protein diffusion into the retina, whether or not there is serous detachment. Where serous fluid exists (e.g., in CSC or under a rhegmatogenous detachment) there is a ready source of subretinal protein to enter the retina and cause edema (Figure 3), although such edema may not be seen clinically on angiography because fluorescein in the subretinal space masks diffusion into the retina. Retinal edema in CSC has been confirmed to occur using ocular coherence tomography [15].

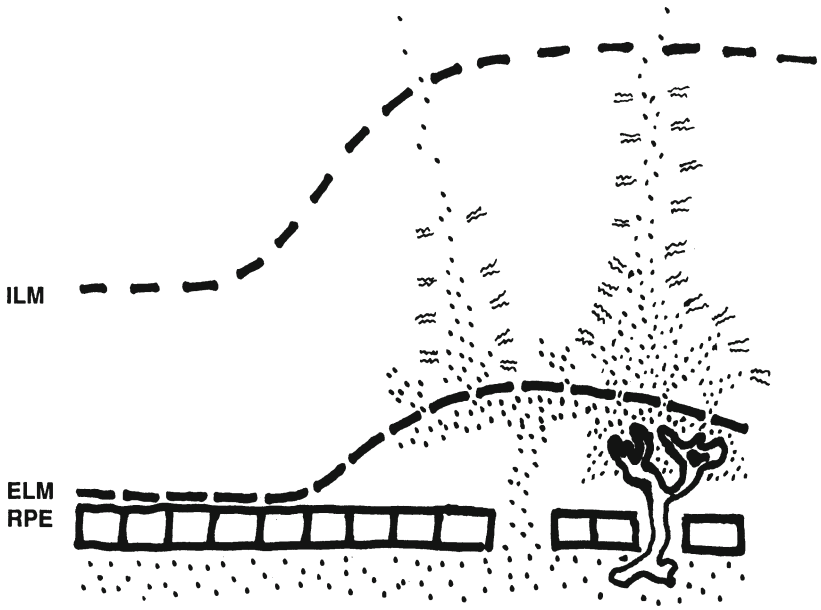

Figure 3. Diagram of edema over a serous detachment or subretinal neovascular membrane. Protein in the subretinal space crosses the ELM in relation to its concentration gradient. The leakage is especially great over subretinal vessels (on the right) that may create a pressure head as well as a high local concentration of protein.

In disorders with subretinal neovascularization (SRN), there is a vigorous source of exudation within the subretinal space which can create a fluid pressure gradient as well as a diffusion gradient for protein. As a result the amount of protein movement into the retina, and the resulting degree of edema, will be even greater than in disorders that damage the RPE barrier without SRN (Figure 3). Since the surrounding RPE may be relatively intact and capable of transporting fluid, classic SRN is often accompanied by only a very small local serous detachment (which lights up immediately on fluorescein angiography), while causing a lot of retinal edema (because the RPE pump cannot directly reach the fluid). In cases of AMD that do have large serous detachments one will generally find a broad area of occult membrane, or a broad zone of age-related pathology, that compromises fluid absorption across the RPE.

Diagnostic and functional implications of edema

Although it may seem intuitively obvious that fluorescein leakage reveals edema, and that edema causes cellular damage and visual dysfunction, neither

assumption is automatically correct. Fluorescein is only about 80% bound to albumin and much of the fluorescence we observe clinically is free fluorescein which is a molecule of only 376 MW. Indocyanine green (ICG), on the other hand, binds very completely to high and low density lipoproteins which are larger than albumin [16]. Free fluorescein is too big to be an accurate marker for water diffusion (although it will go along with water flow), and it is much too small to be an accurate marker for proteins such as albumin. Since free fluorescein can pass through channels that do not admit protein, 'leakage' on fluorescein angiography does not always or necessarily indicate protein leakage or edema. Recent studies using optical methods to analyze retinal thickness (e.g., ocular coherence tomography and the Retinal Thickness Analyzer) have shown that fluorescein leakage also does not always correlate with retinal thickness [17]. Some areas of fluorescein leakage have little edema, perhaps because the barrier damage is only modest and the small molecules are moving quickly through the retina without holding much water. Alternatively, some areas of thickening show little leakage, perhaps because there is swelling of cells more than an accumulation of extracellular fluid. It is possible that other dyes will prove to have more specificity for edema-related leakage, but fluorescein and ICG angiography should not be abandoned yet because they do reveal many types of RPE and vascular pathology and are signature markers for certain disease states. One simply must be aware that fluorescein and ICG leakage are not necessarily equivalent to albumin leakage.

The relationship of edema to changes in visual function is similarly complex. Tissue swelling does not automatically translate into neuronal dysfunction, while the underlying causes of edema (i.e., ischemia) may affect neurons quite independently of the degree of edema. More careful focal evaluation of the retina with techniques such as microscotometry, microadaptometry, and multifocal ERG may eventually lead to a better understanding of the spatial and temporal relevance of edema to the dysfunction of specific retinal neurons and to the development of visual loss.

Therapeutic implications

Three conditions must be present for extracellular edema fluid to accumulate. The first is disease that damages the BRB so that fluid and protein are released; the second is the presence of anatomical features that limit protein and water movement out of the retina so that fluid is retained; the third is inability of fluid absorptive forces to reach or handle the water load. Therapy can be directed at any of these elements.

In general it is preferable to prevent disease rather than treat it, and the ideal therapy for retinal edema is not to let it occur. This can sometimes be achieved by aborting BRB damage through management of an underlying disease (such as improving diabetic control or eliminating an ischemic condition) or by interference with the biological systems that cause BRB opening (such as administering anti-inflammatory agents). A second approach is to alter the physical conditions that favor the accumulation of edema fluid. This would include interventions that remove barriers to the diffusion of water (possibly one effect of laser photocoagulation) or that improve the removal and degradation of protein (possibly another effect of laser treatment). Finally, therapy can be directed towards enhancement of the absorptive forces. Elevated intraocular pressure may increase the passive clearance of water out of retinal tissue, and acetazolamide may improve water transport across the RPE. However, strategies to stimulate RPE transport will work only to the extent that the RPE has access to the fluid and has an ability to increase its rate of transport.

It is instructive in this context to examine the phenomenon of edema resolution after grid laser photocoagulation. This treatment modality remains one of the most effective against different etiologies of edema, although it is not yet clear by which mechanism or mechanisms it works. Table 1 gives a very hypothetical (and undoubtedly incomplete) list of possible laser effects and mechanisms of action. As the relative importance of these different possibilities becomes more clear, one may be able to find less destructive means of accomplishing the same end, or at the least learn how to apply laser therapy in the most specific and effective way.

Summary and conclusions

Retinal edema has its inception in disease that causes a breakdown of the BRB and/or a breakdown of cellular membrane integrity within the retina. From a clinical standpoint there is usually damage to the BRB, and it is important to understand how this leads to tissue swelling. Edema develops not only because there is protein and fluid entering the extracellular space, but because the retinal stroma and ELM limit the clearance of large osmotically active molecules. These molecules bind water osmotically and cause edema. Most edema-causing diseases involve a degree of damage to both retinal and RPE barriers. Better diagnostic tools are needed since fluorescein angiography does not directly measure either fluid movement or protein extravasation, and anatomic measures of tissue swelling do not necessarily show pathophysiology or correlate with visual effects. Therapy may attack either the causes of leakage, the physical conditions that allow fluid accumu-

Table 1. Possible mechanisms of grid photocoagulation therapy

I.	*Reduction of edema-causing pathology:*
	• Improvement in retinal oxygenation which reduces ischemia and metabolic damage
	• Destruction of leaky retinal and choroidal capillaries
	• Debridement and eventual closure of RPE barrier defects
	• Lessened secretion of inflammatory or cytotoxic factors
	• Induction of reparative factors
II.	*Modification of physical factors that favor edema:*
	• Opening of the RPE barrier, to improve water and protein egress from the subretinal space
	• Disruption of the ELM to reduce retinal flow resistance and stop the back-up of protein
	• Alteration of Bruch's membrane to dissipate lipids that block water and protein absorption
	• Stimulation of the clearance of intraretinal protein by phagocytosis
III.	*Improvement of water absorption:*
	• Facilitation of passive water absorption into the choroid
	• Induction of growth of new, healthier RPE cells that transport water more effectively
	• Restoration of metabolic conditions that favor outward RPE water transport

lation, or the active and passive transport systems that enhance fluid removal. Normal RPE transport has a high capacity for pumping water, but the flow resistance of the retina limits water availability to the RPE and may to some degree limit treatment strategies based on RPE transport. The management of macular edema should improve as we learn more about the mechanisms by which it occurs.

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Regulators of vascular permeability: potential sites for intervention in the treatment of macular edema

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Abstract. Rather than being a non-specific reaction to a noxious stimulus, breakdown of the capillary blood-retinal barrier causing macular edema appears to be dependent on a number of active processes which may be open to pharmacological manipulation. Extracellular influences which may affect barrier function include serum and neighboring cell types, which act though cytokines, such as vascular endothelial growth factor and transforming growth factor-ß, and other factors. A number of intracellular pathways acting on the cytoskeleton and components of the intercellular junctional complexes have been identified which mediate agonist-induced leak of the vascular endothelium. The further elucidation of these processes may be useful in the development of better treatments for breakdown of the inner blood-retinal barrier.

Key words: blood-retinal barrier, drug therapy, endothelium, vascular, permeability, protein kinase C, tyrosine phosphorylation

Introduction

Increased permeability of vascular endothelium may occur by two broad mechanisms. Transport of substances between cells is referred to as paracellular transport. Transcellular transport, the other type, is an energy-requiring, largely receptor-mediated (some non receptor-mediated bulk movement may occur through vesicles) process whereby substances are carried through the cell. Most authorities agree that increases in the permeability of vascular endothelium, at least in response to inflammatory mediators, occur mainly via the paracellular route [1].

Paracellular permeability appears to be controlled by a dynamic equilibrium between the tethering forces of the inter-endothelial cell junctional complexes on the one hand and the contractile forces of the cytoskeleton on the other. A number of extracellular influences may modulate this interaction, including factors derived from the serum and neighboring cell types such as pericytes, astrocytes and microglial cells (Figure 1). Whilst VEGF is currently thought to be the major cytokine which leads to breakdown of the blood-retinal barrier [2], we believe that TGFß may also play a part. The identity of cytokines or factors which tighten the barrier is less clear. Potentially inhibitable enzyme systems which are believed to transduce these

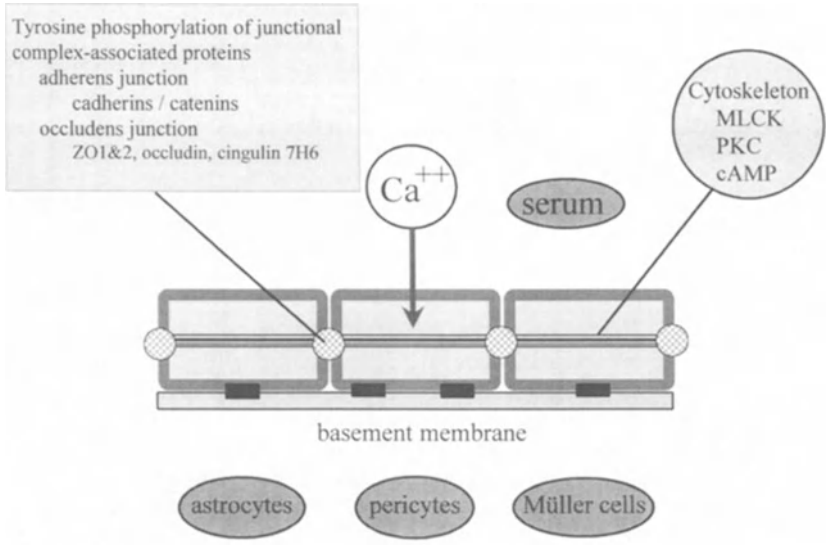

Figure 1. Diagrammatic representation of putative extracellular (dark shading) and intracellular (light shading) regulators of the paracellular permeability of retinal vascular endothelium. MLCK = myosin light chain kinase; PKC = protein kinase C; cAMP = adenosine 3′,5′ cyclic monophosphate; ZO = zonula occludens.

signals include the serine/threonine kinases, protein kinase C (PKC) and myosin light chain kinase, as well as unidentified tyrosine kinases which may facilitate intercellular gap formation by phosphorylating proteins associated with junctional complexes. Intracellular [Ca^{++}] and cyclic AMP levels also appear to be involved. The Figure is a diagrammatic representation of the putative influences on the permeability of retinal vascular endothelium which are the subject of this paper.

In vitro models have been developed to study the paracellular permeability of brain and retinal microvascular endothelium under various conditions [3]. Bovine brain microvessel endothelial monolayers have been shown to retain many biochemical and ultrastructural properties of the blood-brain barrier *in vivo* [4]. Isolated vascular endothelium is grown on polycarbonate membranes coated with basement membrane components such as fibronectin in two chamber systems. The principal assays of barrier function include the trans-monolayer electrical resistance, a measure of the permeability of monolayers to electrolytes which has been correlated with the amount and complexity of tight junctions between epithelial cells [5], and the equilibration across monolayers of macromolecules, such as inulin, which traverse the endothelium exclusively by the paracellular pathway. We and others have shown that bovine retinal capillary endothelial cells cultured in such a system

exhibit paracellular permeability which is an order of magnitude 'tighter' than that attained by cells derived from the peripheral vasculature [6, 7].

Extracellular influences

Neighbouring cells

Astrocytes appear to secrete a factor which induces a high degree of barrier function in microvascular endothelial cells derived from the brain [8]. We have examined the barrier function of human vascular endothelial cells from the retina, choroid and foreskin exposed to conditioned medium from pericytes, astrocytes and retinal pigment epithelial cells [9]. Cells derived from the retinal capillaries achieved a greater electrical resistance compared with cells from the choroid or foreskin, which were similar. All cells behaved in a similar way when exposed to conditioned medium from the other cell types. Astrocyte conditioned medium induced tightening of the endothelial barrier which was maximal six days after its addition. Pericyte conditioned medium caused a modest but significant tightening of the barrier with a delayed maximal effect at ten days after addition to the permeability assay. Conditioned medium from retinal pigment epithelial cells, by contrast, caused a rapid disruption of the barrier with electrical resistance falling to negligible levels within two days. Gardner et al. have also reported the tightening of barrier function of bovine retinal capillary endothelial cells by astrocyte conditioned medium in a similar system to ours which was associated with increased expression of ZO-1 [10]. These studies support the concept that pathways exist by which exogenous factors may reduce leak across the blood-retinal barrier.

Serum

Serum is another source of potential barrier tightening substances. We are currently investigating whether there is a factor in human serum which might exert a trophic effect on the blood-retinal barrier. Serum fractionated by gel filtration contains two peaks of barrier enhancing activity, one associated with albumin and another in a molecular weight range much smaller than that of proteins [11]. Further study has found that this barrier enhancing activity, which is insensitive to heat treatment and trypsinisation, can be dissociated from serum proteins by incubating for 6 hours at 37 °C in the presence of high NaCl ($>0.6\ M$) and high pH (>9.5) (Langford-Smith J, Gillies M, Billson F, unpublished data). The identification of such a factor in serum may be useful not only in the treatment of macular edema but also in explaining the variable

susceptibility to developing macular edema of individuals with diseases such as diabetes.

Cytokines

Whilst most cytokines, such as VEGF, TGFß and TNF reduce barrier function in this assay, interferon alpha 2 (IFN) is the only cytokine tested which improves barrier function [12]. Addition of 50–1000 I.U. of IFN resulted in a marked increase in the electrical resistance of the monolayers with a reduction in the permeability of inulin in the same dose range. It is interesting that the barrier-tightening effect of IFN was achieved despite its anti-proliferative effect on endothelial cells. Other maneuvers to inhibit cell proliferation, such as the addition of TGFß or the use of medium with only 1% serum, led to a loss of barrier function. Whether IFN plays a physiological role in vivo has not been established. The data do provide, however, further evidence for the existence of pathways in retinal capillary endothelium which might be exploited for the treatment of macular edema.

Intracellular signal transduction

Tyrosine phosphorylation

Phosphorylation on tyrosine accounts for only 0.01% of intracellular phosphorylation of proteins. Receptor protein tyrosine kinases (PTKs) are responsible for transmembrane signaling, whereas non-receptor PTKs participate in intracellular signal transduction including pre-and post-translational events. The enhanced activity of PTKs in non-malignant proliferative and inflammatory diseases has led to the development of potential targets for drug design [13].

The reduction in intercellular adhesiveness caused by tyrosine phosphorylation of proteins associated with intercellular junctional complexes is a potentially inhibitable mechanism which may increase the paracellular permeability of vascular endothelium. Adherens junctions are major subcellular targets for tyrosine specific protein phosphorylation [14]. V-src-mediated tyrosine phosphorylation of fibroblasts disrupted the cadherin-mediated aggregation of metastatic fibroblasts [15] and inhibition of tyrosine-specific phosphatases by H_2O_2 and vanadate led to increased expression of phosphotyrosine at the cell borders and a rapid deterioration of intercellular adherens junctions in MDCK cells [16].

A number of proteins are associated with tight junctions, the anatomic correlate of the blood-retinal barrier, which are potential candidates for tyrosine phosphorylation. These include ZO-1 (a+ and a- isoforms), ZO-2, a 130

kDa phosphoprotein which associates with ZO-1 and ZO-2 , cingulin and occludin. As well as these, the cadherins are the major membrane proteins of the nearby adherens junctions, the integrity of which is required for the formation of tight junctions of low permeability [17]. The cytoplasmic tail of the cadherins is linked to the actin cytoskeleton by α-, β- and γ-catenin [18]. Phosphorylation of adherens junction proteins and cytoskeletal components of vascular endothelial cells *in vitro* has been shown to be associated with increased paracellular permeability [19]

We have studied the role of tyrosine phosphorylation of junctional complex-associated proteins in the increase in paracellular permeability of retinal capillary endothelial cells induced by TGFß$_1$ (Gillies MC, Stayt J, manuscript submitted for publication). As well as representing a novel mechanism of vascular leak, responses induced by TGFß are particularly interesting in this context since its receptor is a serine/threonine kinase, in contrast to most other cytokines acting on vascular endothelium whose receptors are tyrosine kinases. Drug inhibition of tyrosine phosphorylation of junctional complexes is thereby easier to separate from inhibition of receptor PTKs, a less specific process which would likely be more toxic in vivo. Immunohistochemical studies revealed that tyrosine phosphorylation of BRCEC monolayers appeared at zones of intercellular contact within 30 minutes of exposure to TGF-β_1. Increased phosphorylation on tyrosine of proteins recognized by antibodies to E-cadherin, α-, β- and γ-catenin, but not ZO-1, was demonstrated by immunoprecipitation of the lysates of cells exposed to TGFß. The increase in permeability was attenuated by the PTK inhibitor herbimycin, and mimicked by orthovanadate, a tyrosine phosphatase inhibitor. VEGF has been shown to have a similar action in vascular endothelium by inducing tyrosine phosphorylation of the non receptor PTK, p125 focal adhesion kinase as well as paxillin, a focal adhesion associated protein [20]. The changes were not, however, correlated with an effect on permeability. We are currently screening a range of tyrosine kinase inhibitors on TGFß- and VEGF-induced increases of retinal endothelial permeability in order to identify candidate drugs for clinical use.

Protein kinase C

Receptor activation by cytokines and inflammatory mediators results in activation of G proteins and phospholipase C. It appears that the protein kinase C (PKC) family of serine/threonine kinases plays an important upstream role in mediating increases in endothelial permeability [21]. There are at least ten isoforms of PKC in mammalian tissue, falling into at least two classes. The 'conventional', Ca^{++}-dependent group comprises the α, β_I, β_{II} and γ isoforms, while the other isoforms make up the 'novel', Ca^{++}-independent

group [22]. Bovine retinal capillary endothelial cells and pericytes are reported to contain the α and β_{II} isoforms [23]. PKC activation has been found to increase the permeability of endothelial monolayers from peripheral tissue [24] and granulation tissue [25]. Other studies have shown that inhibition of PKC attenuates the thrombin- or PMA-induced increases in endothelial permeability *in vitro* [26].

These studies complement experiments on epithelial cells in *vitro*, where PKC activation appears to play a leading role in the dissociation [27] and reassembly [28] of tight junctions, the component of the junctional complex responsible for the 'tightness' of the blood-retinal barrier. Although the nature of the specific target substrates of PKC in vascular endothelium needs further study, the phosphorylation by PKC isozymes of cytoskeletal proteins such as vinculin, caldesmon and vimentin [29, 30] is likely to be involved. Activation of PKC is associated with cytoskeletal rearrangement [31] which is a major influence on cell-cell and cell-matrix adhesion [32].

It has been proposed that activation of PKC may contribute to the pathogenesis of diabetic complications [33]. Although increased activity of the polyol pathway could, theoretically, increase PKC activity [34], elevation by high glucose of diacylglycerol (DAG), a physiological activator of PKC, in bovine retina, aorta and aortic endothelium does not appear to be affected by inhibition of aldose reductase [35]. This would be consistent with our own experience in which increases of paracellular permeability of retinal endothelial monolayers could not be prevented by inhibition of aldose reductase [36]. VEGF-induced increases in retinal leak in rodents were associated with activation of PKC α, β_{II} and δ and almost completely inhibited by an orally effective PKC beta-specific inhibitor [2]. The source of the VEGF *in vivo*, and whether activation of PKC in this context occurs principally in endothelial cells, or also in other cells such as astrocytes and pericytes with secondary pathways leading to the endothelium, has yet to be determined.

Adenosine 3′,5′ cyclic monophosphate

Adenosine 3′,5′ cyclic monophosphate (cAMP) is an intracellular enzyme which increases the tightness of vascular endothelium. ß adrenoceptor agonists such as formoterol increase cAMP which, through activation of protein kinase A, results in relaxation of the cytoskeleton and reduction in permeability [37]. Increases in permeability induced by inflammatory mediators can be inhibited through this mechanism [38].

Calcium dependence

The importance of intracellular [Ca^{++}] ([$Ca^{++}]_i$) in induced increases of vascular endothelium is well established. Restriction of Ca^{++} influx inhibits basal and agonist-induced increases in vascular permeability *in vivo* and *in vitro* [39, 40]. Chelation of $[Ca^{++}]_i$ leads to relaxation of the cytoskeleton and reduction in endothelial permeability by attenuating the phosphorylation of myosin light chain by myosin light chain kinase [40]. Calcium ionophores produce other intracellular changes which may also affect permeability, including a reduction in the level of intracellular cAMP [41]. Increased $[Ca^{++}]_i$ has been associated with an increase in phosphorylation of cytoskeletal proteins [42]. Both the activation of classical PKC isozymes and the homophilic interaction of cadherins in intercellular adherens-junctions are also calcium-dependent process. Unfortunately it appears that the entry of Ca^{++} into vascular endothelium does not occur through voltage gated channels [43] so the process may not be susceptible to manipulation with calcium channel blocking drugs.

Conclusion

Specific drug treatments are likely to become available for macular edema in the foreseeable future. The results of clinical trials of protein kinase C inhibitors, which have shown promise in animal studies of diabetic retinopathy, are awaited with interest. Inhibitors of protein tyrosine kinases are in earlier phases of development. Continued research into the intracellular and extracellular mechanisms which control the paracellular permeability of the retinal vascular endothelium is likely to result in improved strategies for the medical treatment for macular edema which will be helpful either alone or in combination with photocoagulation.

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Inhibition of membrane-bound carbonic anhydrase decreases subretinal pH and volume *

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Abstract. *Purpose:* The lipophilic carbonic anhydrase (CA) inhibitor acetazolamide has been shown to enhance subretinal fluid resorption, reduce subretinal pH, and can improve cystoid macular edema, but its clinical use is limited by systemic side effects. While these are most likely a result of inhibiting intracellular CA isoenzymes, retinal pigment epithelial (RPE) transport is thought to be modulated via membrane-bound CA. This study investigates whether benzolamide, a hydrophilic CA inhibitor that does not readily penetrate cell membranes, is sufficient to modulate subretinal volume and pH. *Methods:* Volume and pH were assessed in the subretinal space (SRS) of the perfused chick retina–RPE-choroid preparation by calculating these variables from data obtained with two different double-barreled, ion-selective electrodes (H^+ for pH and the extracellular space marker tetramethylammonium (TMA^+) for SRS volume). Light induced variations and changes in baseline measurements were recorded before and after addition of 10^{-4}M acetazolamide or benzolamide to the basal perfusion. *Results:* Basal perfusion with either drug induced both an acidification of the SRS by 0.02–0.04 pH units, which occured within 60 s, as well as an increase in the amplitude of the light-induced alkalinisation of the SRS. TMA^+ concentration in the SRS increased steadily over a period of several minutes after basal perfusion with either of the CA inhibitors, and the calculated SRS volume was reduced by 40% within 8–10 min. *Conclusion:* The observation that benzolamide had effects equal to acetazolamide suggests that inhibition of membrane-bound CA at the basolateral membrane of the RPE is sufficient to decrease subretinal pH and volume. This may represent a clinically important mechanism for the resorption of sub- and intraretinal fluid.

Key words: carbonic anhydrase, subretinal space, pH, retinal pigment epithelium

Introduction

The lipophilic carbonic anhydrase (CA) inhibitor acetazolamide has been

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shown to enhance subretinal fluid resorption [1] and reduce subretinal pH [2]. It has been postulated that this modulation of fluid resorption may be linked to changes in H^+ or HCO_3-transport on the apical membrane of the retinal pigment epithelium (RPE) [2, 3]. In recent years several authors have also reported a beneficial effect of acetazolamide in the treatment of cystoid macular edema (CME) [4–8], although its clinical use is limited by systemic side effects [9]. While these side effects are most likely a result of inhibiting intracellular CA isoenzymes [10], retinal pigment epithelial fluid transport is thought to be modulated via *membrane-bound* CA both in humans [11, 12] and in chicks [13]. This isoform of CA appears to regulate and modulate the extracellular pH gradients created by the metabolic activity of cells and may act as a bicarbonate channel [14].

This study investigates whether benzolamide, a hydrophilic CA inhibitor which does *not* readily penetrate the cell membrane due to a very high degree of ionization and protein binding [15–19], has similar effects like acetazolamide on retinal pigment epithelial functions, i.e., on the modulation of subretinal pH and volume.

Materials and methods

Experiments were carried out on 2–7-day-old *Gallus domesticus* chicks (n=25). All animals were treated according to the ARVO resolution on the Use of Animals in Research. The chicks were dark adapted and the eyes enucleated in the dark and placed in a 95%/5% O_2/CO_2 bubbled bath. A full thickness section of retina, RPE and choroid (approximate diameter, 5–7 mm) was carefully dissected from the globe, spread on a mesh grid and placed retinal side up between two lucite plates in an Ussing perfusion chamber (Figure 1). The control perfusate contained 5.0 mM $(CH_3)_4NCl$ tetramethylammonium as well as 115.0 mM NaCl, 1.8 mM $CaCl_2$ and was constantly oxygenated with 95% 0_2/5% CO_2, maintaining the pH at 7.5±0.1 and the temperature at 36.0±1.0°C. Because of its large size, charge and relative cell membrane impermeability tetramethylammonium (TMA^+) is an appropriate extracellular space marker which has been used to investigate light-induced volume changes in frog [20], in cat [21] and chick retina [22] as well as volume changes in the brain [23, 24].

Double-barreled, ion-selective microelectrodes were fabricated using a technique described previously [25]. Briefly, the ionselective barrel was silanised for 2 min by dimethyl-dichlorosilane, filled with Corning 477317 ion-exchanger resin in its tip (Corning Medical and Scientific, Medfield, MA) and was then backfilled with a simplified Ringer solution containing (in mM) 120.0 NaCl, 5.0 KCl, and 1.8 $CaCl_2$. The reference barrel was backfilled with

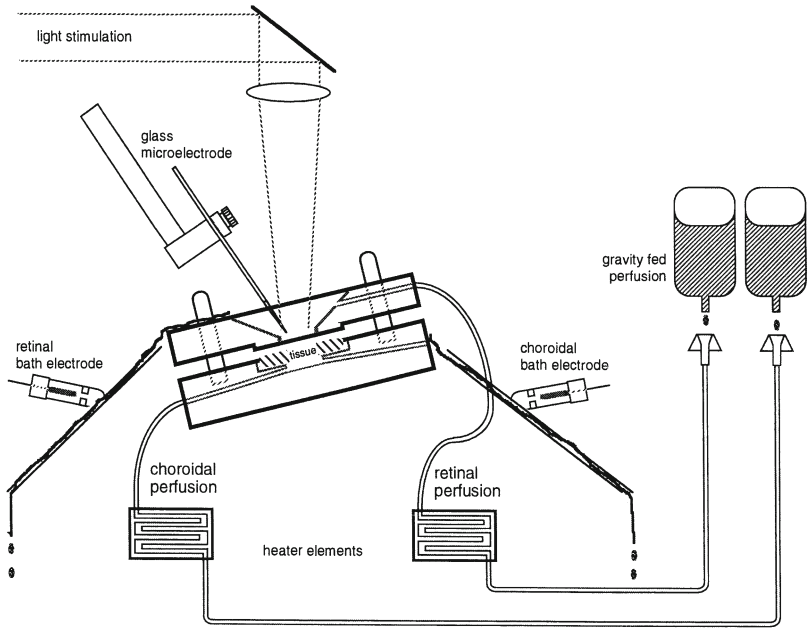

Figure 1. Ussing chamber with apical (retinal) and basal (choroidal) perfusions. The position of the ion-selective electrodes was controlled by measuring the light induced transtissue, transretinal and trans-RPE potentials.

the same solution. The resistance of the ion-selective channel was 10–30 gΩ. All microelectrodes were calibrated just before and immediately after each experiment in the perfusion chamber at 36°C. The tip diameter was 5–10 μm. The TMA^+ to K^+ selectivity of these electrodes has been determined at 180:1 to 190:1 [21]. To measure pH, the ion-sensitive barrel of the electrodes were filled with Fluka #95291 (Hydrogen Ionophore I, Cocktail A). The tissue was first equilibriated during constant perfusion and remained dark adapted in the Ussing chamber for at least 1 h before the electrophysiological recordings were started. The diffuse white light stimulus was provided by a halogen lamp with an intensity on the tissue surface of 6×10^{-5} W/cm^2.

Subretinal recordings were obtained by placing the H^+ or the TMA^+ selective electrode in the subretinal space (SRS) by advancing the electrode from the vitreal surface of the neural retina perpendicularly to the tissue in 20-μm steps. By referencing the nonselective barrel to the retinal (apical, see legend for Figure 1) and choroidal (basal) surface, the transretinal and transepithelial potential could be measured respectively (Figure 2). They served as an indicator of the microelectrode position in the retina. Reaching the SRS was determined either by monitoring the transretinal and the transepithelial c-wave potential that could be obtained by a 1-s flash every

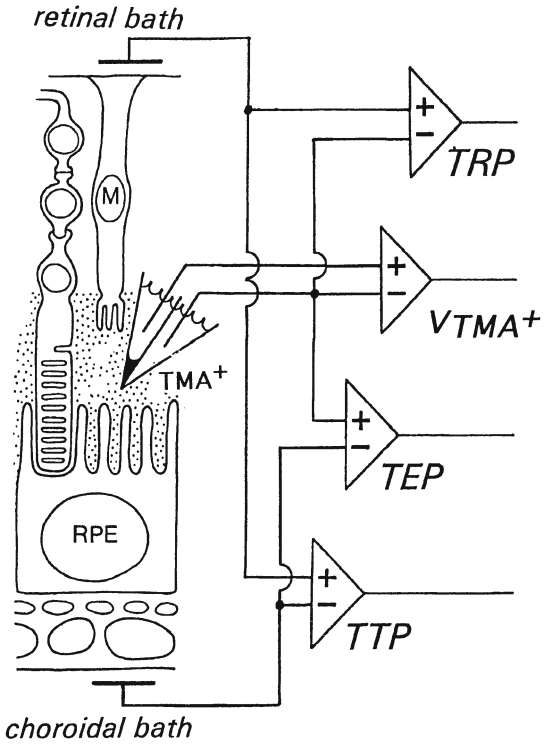

Figure 2. Configuration for the recording from the chick choroid–RPE-retina preparation. Double-barreled electrodes were positioned in the SRS. Referencing the nonselective barrel to the retinal and choroidal baths, the transretinal potential (TRP) and the transepithelial potential (TEP) are recorded differentially. $V_{(TMA^+)}$ is the differential signal between the TMA^+ barrel and the reference barrel and is a measure of the local TMA^+ concentration in the extracellular space of the retina (including the SRS). The transtissue potential (TTP) is recorded differentially between the retinal and choroidal baths.

60 s until constant maximal amplitudes were recorded, or by penetration of the RPE as indicated by an abrupt change of the potential in the reference channel. This was followed by retracting the electrode 10–20 μm to place it in the SRS.

Once the electrode was placed in the SRS, light reactions were recorded to check the functionality of the sample. Then the apical or basal perfusate was changed to a solution containing a 10^{-3}or 10^{-4}M acetazolamide or 10^{-3}or 10^{-4}M benzolamide. The measure of ion activity for H^+ and TMA^+ was indicated by the differential voltage between the ionselective and reference barrels. Recorded signals were displayed on a computer monitor and stored in a personal computer for subsequent analysis. Data digitization (8 Hz) and

storage were controlled by Labtech Notebook software (Scientific Solution, Wilmington, MA).

Results

As observed earlier [2], illumination induced transient alkalinisation of the SRS (data not shown). When applied in darkness, 10^{-3}M of acetazolamide in the basal perfusate reduced the pH in the SRS by 0.052, and 10^{-4}M by 0.034 pH units. A dose of 10^{-3}M of benzolamide induced an acidification of the SRS of 0.037 and 10^{-4}M of 0.032 pH units (Figure 3a,b). The acidification in the SRS occured about 60 s after adding the drugs to the perfusate. Both acetazolamide and benzolamide increased the light induced alkalinisation of the SRS. Both CA inhibitors also induced a slow increase in the SRS TMA+ concentration indicative of the volume decrease in that compartment (Figures 4a and 5a, uppermost traces). However, direct TMA^+ measurements only show the direction of volume changes but strongly distort their magnitude and time course due to the diffusion of the extracellular marker [22]. Thus the calculation of SRS volume was performed by using the mathematical model developed by Govardovskii et al. [22]. Model computations show that corresponding changes in subretinal space volume occured over a much more extended period of 8–10 min after application of the drugs. A dose of 10^{-3}or 10^{-4}M acetazolamide in the basal perfusate decreased SRS volume by over 40% (Figure 4b, lower trace). By adding 10^{-3}or 10^{-4}M of benzolamide to the basal perfusate, SRS volume decreased also by 40% (Figure 5b, lower trace). None of these changes could be induced by adding either of the two carbonic anhydrase inhibitors to the apical perfusate.

Discussion

We have identified a similar action of acetazolamide and benzolamide on RPE-modulated regulation of SRS pH and volume. This observation suggests that inhibition of membrane-bound CA at the basolateral membrane of the RPE is sufficient to decrease subretinal pH and volume, and may represent a clinically important mechanism for the resorption of sub- and intraretinal fluid.

The fastest changes after administration of the drugs were a hardly visible decrease in the standing potential and a more marked reduction in SRS pH. The former data confirm previous observations of a decrease of the TEP after administration of acetazolamide in man, rabbit and frog [26–29]. Changes in the standing potential of the RPE result from changes in the apical or

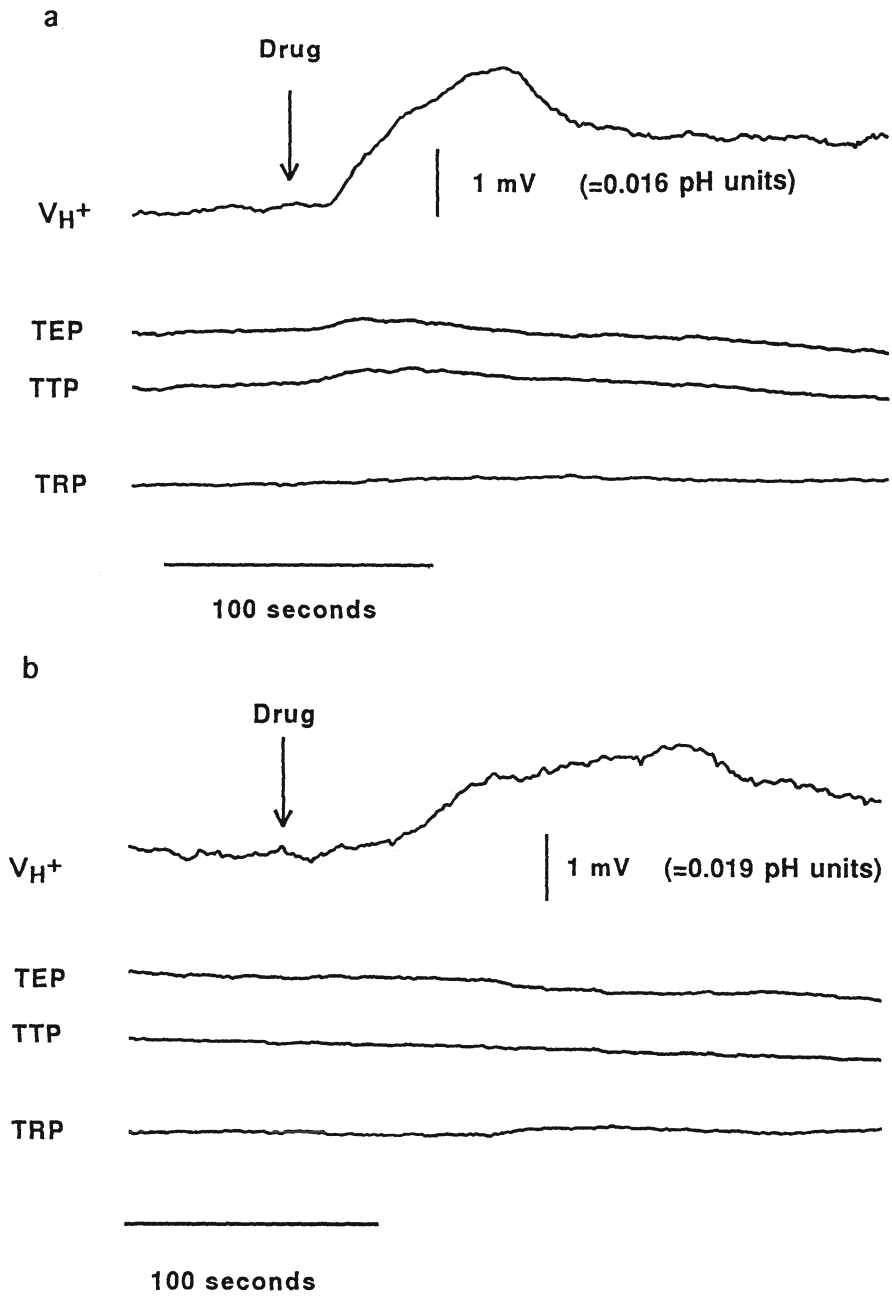

Figure 3. (a) Effect of 10^{-4}M acetazolamide on the potential of the H^+-selective electrode (V_{H^+}) in the subretinal space after administration to the basal perfusion. Note a swift change in pH over a period of about a minute. There is a very weak decrease in TEP and TTP. The acidification in the SRS amounts to 0.034 pH units. (b) Effect of 10^{-4}M benzolamide on the potential of the H^+-selective electrode (V_{H^+}) in the subretinal space after administration to the basal perfusion. Note a swift change in pH over a period of about a minute. There is a very weak decrease in TEP and TTP. The acidification in the SRS amounts to 0.032 pH units.

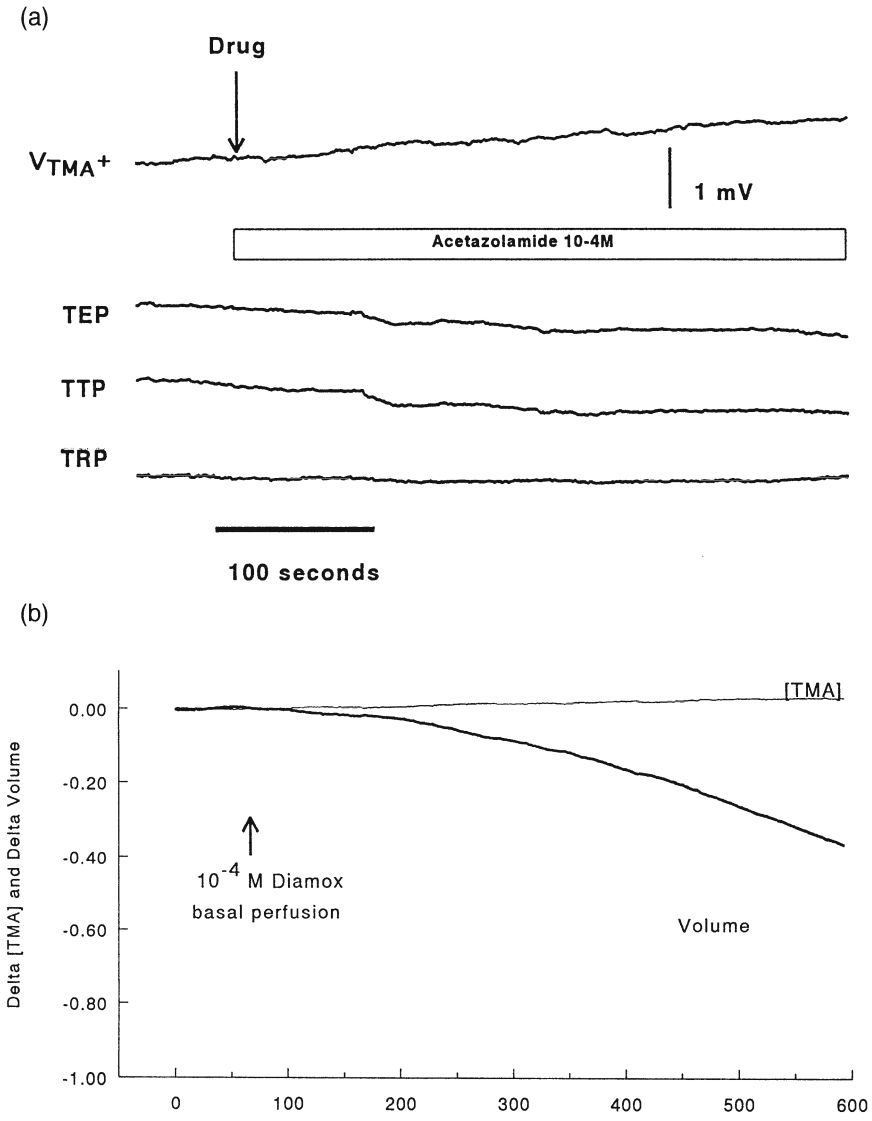

Figure 4. (a) TMA^+ potential (V_{TMA^+}) after administration of 10^{-4}M benzolamide to the basal perfusion. Note a gradual increase in potential over a period of several minutes. There is a very weak decrease in TEP and TTP. (b) Calculated volume changes (ΔV) in the SRS after the administration of 10^{-4}M benzolamide to the basal perfusion. Subretinal space volume is decreased by over 40% within 10 min.

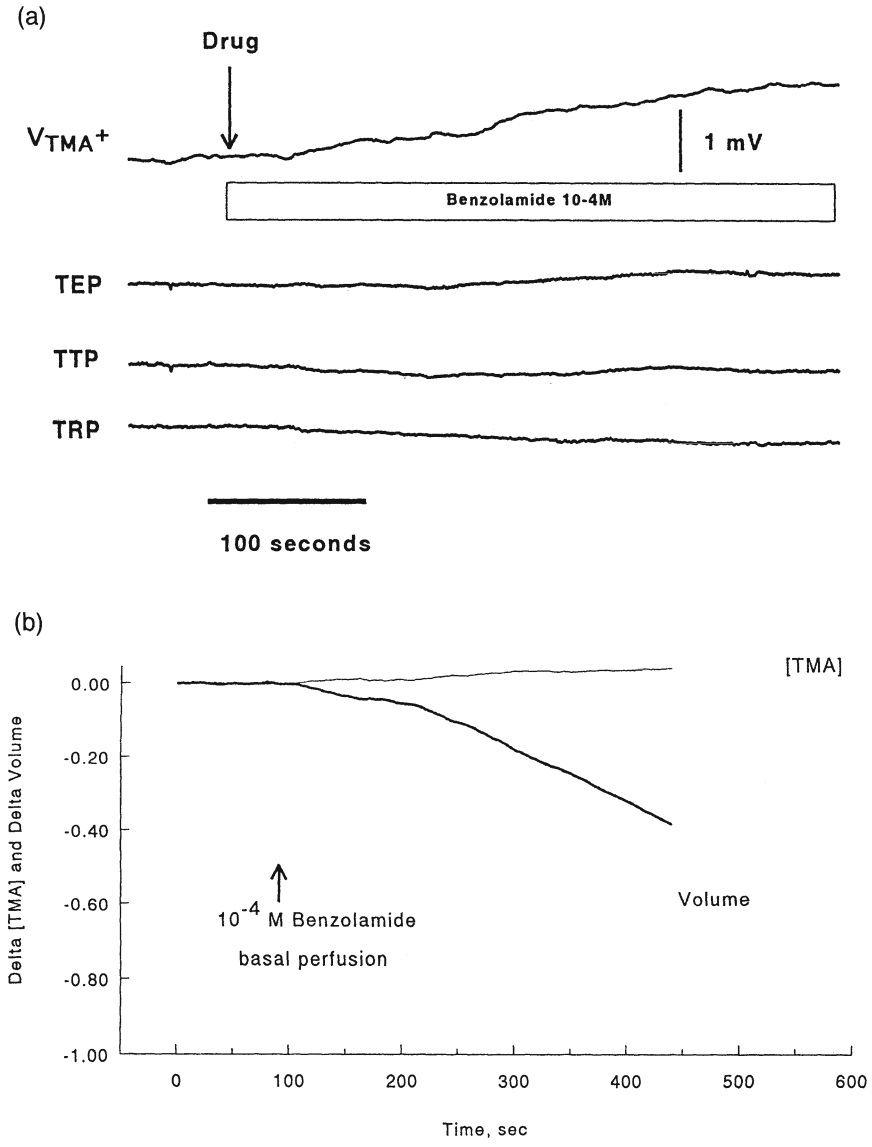

Figure 5. (a) TMA^+ potential ($V_{TMA}{}^+$) after administration of 10^{-4}M acetazolamide to the basal perfusion. Note a gradual increase in potential over a period of several minutes. There is a very weak decrease in TEP and TTP. (b) Calculated volume changes (ΔV) in the SRS after the administration of 10^{-4}M acetazolamide to the basal perfusion. Subretinal space volume is decreased by about 40% within 8 min.

basolateral membrane potential, and basolateral perfusion with acetazolamide appears to hyperpolarize the basolateral membrane, which in turn decreases the standing potential.

The more evident rapid change that we could observe in our preparations was the acidification of the SRS which occurred within 60 s after drug administration. The decrease in pH after application of both acetazolamide and benzolamide confirms previous *in vitro* data obtained in frog using the lipophilic carbonic anhydrase inhibitor methazolamide [30]. The acidification was of the same order of magnitude (0.04 pH units). Similar data have been obtained *in vivo* in cat where an acidification of the SRS by 0.2 pH units occurred within 45 s after intravenous injection of acetazolamide [2]. This acidification was also most pronounced just above the RPE diffusing throughout the retina into the vitreous. It is thought to originate in a change in the transport of H^+ or HCO^{3-} on the apical membrane of the retinal pigment epithelium [2]. These local changes could not be induced by creating a systemic acidosis by other means. The observed increase in light-induced alkalinisation of the SRS after application of both acetazolamide and benzolamide also confirms previous data in frog [30]. The changes in SRS volume occured at a much slower rate than the changes observed in pH or TEP. This is most probably due to the fact that volume changes depend on fluid flow which in turn is effected at a much slower pace than local changes in pH. The fact that adding the CA inhibitors to the apical perfusate did not induce any changes in SRS volume confirmed previous findings in rabbits where acetazolamide administered to the apical side of the RPE had no apparent effect both *in vivo* [31] and *in vitro* [32, 33], whereas intravenous injection of the drug enhanced resorption and retinal adhesiveness [33–35]. It appears thus that the presentation of the drug to the basolateral membrane domain of the RPE is paramount.

Our data showing comparable results with either acetazolamide or benzolamide suggest that inhibition of membrane-bound carbonic anhydrase at the basolateral surface of the retinal pigment epithelium is sufficient to to acidify the SRS and to increase fluid absorption through the RPE with consecutive reduction of the extracellular space volume in the retina. The time course of an immediate pH reduction within about 60 s followed by a gradual decrease in SRS volume over several minutes suggests that SRS acidification acts as the trigger event. This acidification is thought to induce changes in ion flow which, in turn, are followed by fluid movement [3].

In view of these results benzolamide should be as effective clinically as acetazolamide in the resolution of macular edema without incurring the manifold side effects. The preliminary results of a double-blind placebo-controlled

cross-over trial investigating the effects of benzolamide on visual acuity and side effects in patients with macular edema support this hypothesis [8].

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Macular hole formation in diabetic retinopathy: the role of coexisting macular edema

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Abstract. The aim of this study was to characterise different etiologies for the development of macular holes in diabetic retinopathy. We examined 8 eyes of 8 patients with known diabetic retinopathy who had developed a macular hole. These were classified as follows: related to macular edema (4 eyes), non-related to macular edema (2 eyes), intraoperative (1 eye) or postoperative (1 eye) after pars plana vitrectomy for proliferative diabetic retinopathy. In three patients the macular holes were treated with pars plana vitrectomy and fluid air exchange.

In diabetic eyes with macular edema, macular holes may develop because of intraretinal exudation combined with increased vitreomacular attachments and tractions. The mechanism of macular hole formation in diabetic eyes without macular edema probably results from the same increased tangential vitreous traction which is seen in idiopathic age-related macular holes. Iatrogenically induced macular holes during pars plana vitrectomy for proliferative diabetic retinopathy may be also due to intraoperative vitreoretinal tugging. Finally, macular holes developing after vitrectomy may have an etiology not related to vitreous tractions or attachments.

Introduction

It has been proposed that idiopathic age-related macular holes are consequent to tangential vitreous traction and that they may be succesfully treated with vitreoretinal microsurgery [1–5]. Macular holes may also develop following non-penetrating ocular trauma [6], a lightning strike [7] in eyes with congenital retinal arteriovenous malformation [8] and in severe hypertensive retinopathy [9]. Macular holes may also develop in eyes with diabetic retinopathy. To the best of our knowledge, to date only two eyes have been reported in the literature with the combined fundus pathology of diabetic retinopathy and macular hole which were treated with pars plana vitrectomy and prolonged gas tamponade [10]. In our study we report our findings on 8 patients with diabetic retinopathy who developed a macular hole and discuss hypotheses of the pathogenesis.

Patients and methods

We studied retrospectively 8 eyes of 8 patients presenting a diabetic retino-

pathy and a macular hole (5 men and 3 women). Age ranged from 54 to 78 years with a mean of 67 years. Biomicroscopic fundus examination included a detailed examination of the vitreoretinal interface in order to determine the extent of vitreous attachments, and the presence of macular edema. Fluorescein angiography was performed to investigate the presence of macular edema and neovascularisation. The macular holes were classifed into the following 4 categories: related to macular edema, non-related to macular edema, intraoperative iatrogenic complication of pars plana vitrectomy for proliferative diabetic retinopathy, and postoperative complication of pars plana vitrectomy for proliferative diabetic retinopathy.

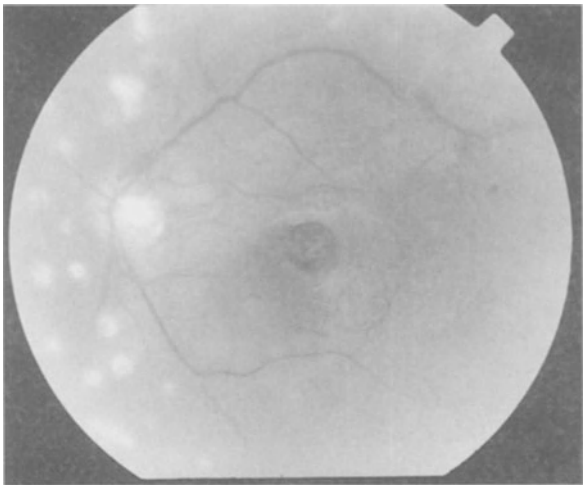
Results

A macular hole was diagnosed in 5 eyes because of progressive central visual loss. It was an intraoperative finding during pars plana vitrectomy in 1 eye, an intraoperative complication of pars plana vitrectomy in 1 eye, and a postoperative complication of pars plana vitrectomy in 1 eye. Six eyes presented with a proliferative diabetic retinopathy (Figure 1). The vitreous in the premacular space was detached in 5 eyes and it was attached in the remaining 3 eyes.

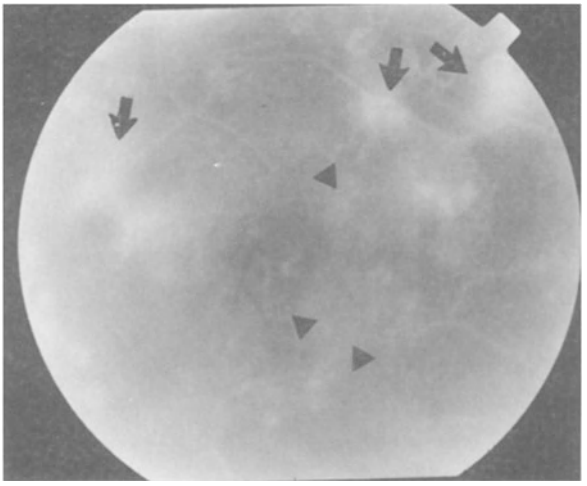
The first diagnostic class with macular holes accompanied with macular edema occured in 4 patients (Figure 1). None of these eyes had *cystoid* macular edema. Three of these eyes had proliferative diabetic retinopathy (Figure 1). In 1 of these eyes the macular hole was diagnosed during pars plana vitrectomy for non-clearing vitreous hemorrhage. Vitreous was detached at the macular area at this eye and postoperatively, following prolonged gas tamponade, the edges of the macular hole were flattened and the hole was not visible. In two of the remaining eyes the macular hole was treated with pars plana vitrectomy, removal of the posterior hyaloid, fluid/air exchange and filling of the eye with 20% SF6. Macular holes were closed in both eyes postoperatively. In one eye visual acuity improved from 20/400 to 20/200 at the 6 months follow-up and in the other eye the visual acuity improved from 20/50 to 20/40 at the 4 months follow-up.

The second diagnostic category included macular holes occurring in eyes with background retinopathy but without macular edema. Two eyes in our study with mild background diabetic retinopathy and attached posterior vitreous presented this type of macular hole.

The third diagnostic category included macular holes induced iatrogenically during pars plana vitrectomy. This occurred in 1 eye with severe proliferative diabetic retinopathy having presented a thickened and fibrotic posterior hyaloid attached to the macula and inducing a tractional macular detachment. During dissection of the posterior hyaloid and of the vitreofoveal attach-



(a)



(b)

Figure 1. (A) Stage 4 macular hole (approximately 3/4 of disk diameter) in a diabetic eye with detached vitreous. Note the photocoagulation scars nasally to the disk and the cuff of subretinal fluid at the borders of the hole. New vessels are visible on the disk. (B) Fluorescein angiogram in the late arteriovenous phase showing a window defect at the level of the macular hole. Arrows show hyperfluorescence due to new vessels and arrowheads denote leakage of retinal capillaries responsible for the diffuse macular edema. Note the ischemic retina temporally.

ments a small macular hole was created. The hole was eventually closed with prolonged gas tamponade.

Finally, the fourth category included macular hole formation as a postoperative complication of pars plana vitrectomy for proliferative diabetic retinopathy. In our study, one macular hole developed 2 months following surgery for nonclearing subhyaloid hemorrhage covering the macula. The macular hole was due to a preretinal and retroretinal macular fibrotic membrane.

Discussion

Macular hole formation is uncommon in patients with diabetic retinopathy. The unique anatomic morphology of the retina at the foveola predisposes this area to full-thickness hole formation after a variety of insults [11]. In addition to the tangential vitreoretinal traction, which have been proposed as the primary cause of idiopathic macular hole formation [1, 2], other important factors may play an important role in macular hole formation in eyes with diabetic retinopathy.

In diabetic eyes with macular edema the intraretinal exudation may result in a cystoid degeneration of the retina that may progress spontaneously to macular retinoschisis (cyst) and even partial or complete macular hole formation [12]. In less pronounced situations of macular edema atrophy of the retina may develop due to pressure built up through the accumulation of fluid in the extracellular space [12]. This may render the retina more vulnerable to vitreous traction. Consequently, macular edema may represent a precursor of macular hole formation in eyes with diabetic retinopathy as seen in 50% of all the eyes in the present study.

Vitreous adhesions are greater at the level of the fovea as evidenced by the higher density of hemidesmosomes in that area [13] and vitreoretinal attachments are equally strong at the level of new vessels in proliferative diabetic retinopathy. A partial posterior vitreous detachment in these eyes may leave residual vitreoretinal tractions in the posterior pole especially if the posterior hyaloid is thickened from previous hemorrhages. Therefore, increased vitreoretinal traction may be an additional predisposing factor to macular hole formation in eyes with proliferative diabetic retinopathy [10]. In our study increased vitreoretinal attachments at the level of macula were observed in all eyes with proliferative diabetic retinopathy, with or without macular edema, that developed a macular hole and also in the eye in which the macular hole was iatrogenically induced during pars plana vitrectomy.

Concerning the 2 eyes without macular edema in which a macular hole developed, we believe that the pathogenetic mechanism is the same as that of idiopathic macular holes, i.e. tangential vitreous traction [1, 2]. Finally,

macular holes in diabetic eyes may occur after pars plana vitrectomy for proliferative diabetic retinopathy. Their etiology may be other than tangential vitreous traction because of the apparent absence of the posterior cortical vitreous in these eyes [14]. In the present study, a macular hole developed in one eye following pars plana vitrectomy for proliferative diabetic retinopathy due to a postoperative macular fibrotic membrane.

Pars plana vitrectomy with fluid/air exchange and prolonged gas tamponade has been used with success to both flatten the cuff of subretinal fluid that surrounds a macular hole and to close the macular break with improvement in visual acuity [3–5, 15]. We treated two eyes with macular hole and diabetic macular edema with pars plana vitrectomy and prolonged gas tamponade and observed a moderate improvement in visual acuity. Prolonged gas tamponade was also performed in another eye in which the macular hole, associated with macular edema, was discovered during pars plana vitrectomy for vitreous hemorrhage. Although there is limited experience with macular hole surgery in eyes with diabetic retinopathy [10] these eyes probably have a poorer prognosis after hole closure because of the additional macular diabetic changes.

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Macular edema in retinal vein occlusion: Up-date from the central retinal vein occlusion study

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Introduction

Cystoid macular edema in retinal vein occlusions is frequently associated with visual loss. Both macular edema and reduced vision may persist for months and no medical therapies have been shown to be beneficial. In the presence of a branch retinal vein occlusion (BRVO) associated with macular edema the Branch Retinal Vein Occlusion Study has shown that grid macular treatment may be effective in reducing macular edema and in improving visual acuity [1].

Several uncontrolled pilot studies have reported similar improvements of macular edema and increase in visual acuity in patients with macular edema associated with central retinal vein occlusion (CRVO) [2–5]. However, spontaneous visual recovery and resolution of macular edema may occur in about two thirds of cases with perfused CRVO. The major goal of the Central Retinal Vein Occlusion Study was thus to evaluate in a randomized clinical trial the use of grid pattern photocoagulation for macular edema in perfused CRVO [6].

Patients and methods

Inclusion criteria were a perfused central retinal vein occlusion of at least 3 months duration, an edema on fluorescein angiogram and a visual acuity of 20/50 or worse. Patients with diabetic retinopathy, age related macular degeneration or previous cataract surgery were excluded. A total of 155 patients was entered into study. Eyes were randomly assigned to either grid laser photocoagulation, or to clinical observation.

Laser treatment was performed using the Argon green laser, 100 micron spots with a duration of 100 ms and one half to one burn width apart. The laser

treatment covered the leaking area outside the capillary free zone as shown by fluorescein angiography. The patients were re-evaluated at 4 months and a careful refraction by personnel certified for this purpose was performed. If no improvement in visual acuity had occured and edema was still present, re-treatment with laser photocoagulation was performed. The median number of laser spots applied was 143. Study data were continuously reviewed every six months by the Data and Safety Monitoring Board.

Results

Of the 155 eyes entered into the study 95% were followed for one year, 75% were followed for two years and 57% were followed for three years. 13% of eyes had incomplete follow-up. There were no laser treatment complications.

Macular edema was significantly reduced as judged by fluorescein angiography after laser treatment. At the 12 month visit, 21 of 68 (31%) of the treated eyes showed no macular edema, whereas 100% of the untreated eyes had macular edema.

There was no significant difference in visual acuity between the two groups. In addition, there was also no difference between the two subgroups of patients who were entered into the study with a CRVO of either longer or shorter than one year duration. The mean change in visual acuity from baseline showed that 33% of treated eyes and 29% of untreated eyes lost at least 2 lines between the baseline exam and the final follow-up visit. 23% of treated eyes and 18% of untreated eyes improved by 2 or more lines. 44% of treated eyes and 53% of untreated eyes remained stable. Initial median acuity was 20/160 in treated eyes and 20/125 in untreated eyes. Final median visual acuity was 20/200 in treated eyes and 20/160 in the control eyes.

The treatment effect seemed to be associated with age. Among the patients who were below the age of 65 years, 50% of treated patients and 30% of untreated patients gained two or more lines of visual acuity. However, among the patients who were above the age of 65 years only 6% of treated patients and 13% of untreated patients gained two lines or more in visual acuity. This marked difference between the age groups represents a strong clinical trend, although when adjustments were made for the fact that it was an unplanned observation, the data were not statistically significant.

Discussion

The Central Vein Occlusion Study has thus shown no beneficial effect on visual acuity from grid laser treatment as compared to observation without

laser therapy. It is curious that there was a marked beneficial effect on macular edema but not on visual acuity.

It can be speculated that the massive macular involvement with diffuse leakage is very different from the small and segmental leakage that occurs in branch vein occlusion. This more diffuse edema may not permit major neural recovery in CRVO patients. Another factor which may explain the difference between the BRVO study and the present study, is the age distribution of the included patients. Almost half (44%) of the patients in the present study were above the age of 70, whereas only 32% were above the age of 69 years in the BRVO study, the Early Treatment Diabetic Retinopathy Study having excluded patients above the age of 70. It could thus be possible that massive diffuse macular edema that occurs in CRVO may damage older neurons more profoundly and inflict irreparable damage that will last even though macular edema is regressing after grid laser photocoagulation.

Recently, our group has suggested that improvement of retinal circulation times may be an important factor to predict an improvement in visual acuity [3]. Based on the present data, grid laser photocoagulation is not recommended for the treatment of visual loss from perfused macular edema. It is possible that grid laser photocoagulation may be beneficial for patients with perfused CRVO who are below the age of 65 years, but the present sample was too small to demonstrate a statistically significant benefit. The observed trend, that age may play a role in the response to laser treatment of macular edema warrants thus further evaluation.

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Visual prognosis of macular involvement in peripheral retinal vascular malformations

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Abstract. The visual prognosis in eyes with and without macular pathology, after treatment of the primary, peripheral retinal vascular malformation (PRVM) was studied. Seventeen patients (16 eyes) underwent treatment of the PRVM with laser/cryopexy. In 13/17 eyes (76.4%) associated macular pathology included, macular oedema and/or hard exudates (5 eyes), epiretinal membrane (2 eyes), exudative retinal detachment (3 eyes), vascular malformation in macula (2 eyes) and macular hole (1 eye). Initial visual acuity ranged from counting fingers 20/200. After treatment of the primary lesion, the visual acuity improved in five eyes, decreased in one eye and remained stable in 7 eyes. Of the four eyes without macular involvement, the vision improved after treatment in two eyes and remained stable in two eyes. We conclude that a variety of macular lesions can reduce central vision in eyes with PRVM. After treatment of only the primary lesion, the macular lesions also show changes. Visual acuity can improve or remain stable after treatment of the primary lesion. Rarely, the vision can decrease.

Introduction

The spectrum of primary retinal telengiectasia is very large. It varies from that seen in young boys and commonly referred to as Coat's disease (or Juvenile telengiectasia) [1–3], to Leber's miliary aneurysm, Reese's retinal telengiectasia [4] and idiopathic juxtafoveolar telengiectasia [5]. Primary peripheral retinal vascular abnormalities in adults characterized by telengiectasis, formation of aneurysms, deposition of lipoidal material and exudative retinal detachments, is also a well known clinical syndrome [6]. Retinal angiomas can occur as solitary tumours in the retinal periphery, usually, though not essentially, as part of the Von Hippel–Lindau syndrome [7, 8].

All the above primary retinal vascular malformations (PRVM) have a common feature of increased vascular permeability which can lead to secondary changes in the macular area, irrespective of their nature or location in relation to the macula. The changes described earlier in such cases include, macular edema, serous retinal detachments, extension of the vascular malformations into the macular area, macular capillary non-perfusion, and epiretinal membranes [3–11]. The visual prognosis in these eyes with macular involvement is not extensively described in the literature, except in isolated case reports.

We studied the effect of treatment of the peripheral retinal vascular malformation (PRVM), on the visual outcome in eyes with macular pathology and compared it to the few eyes that did not have macular involvement.

Materials and methods

A retrospective analysis of all eyes with primary peripheral retinal vascular lesions treated at our hospital from 1991–1997 was performed. Eyes with juxtafoveolar telengiectasis or with telengiectasis secondary to a known disease (e.g. Eale's, diabetes, venous occlusion, etc.) were excluded. We studied 17 eyes of 16 patients with PRVM. All patients had a complete eye examination including fundus photographs and wherever possible, fluorescein angiography. In few eyes where photography was not possible, detailed fundus drawings from the patients' charts, were used for the analysis. All patients underwent treatment with cryotherapy or argon laser photocoagulation or both. In case of bullous retinal detachment, subretinal fluid was drained surgically to allow for the treatment of the vascular lesion with either cryopexy or laser. Additional treatment was performed with the same or a different modality if the lesion did not show scarring or regression 2 months after the initial treatment. Treatment was carried out in multiple sessions until the vascular lesion was clinically and/or angiographically stable, until it regressed, or when it was thought that vision could not be salvaged by further treatment.

In one eye surgical drainage of the subretinal fluid was performed along with scleral buckling before cryopexy of the peripheral angiomas. Patients were followed up every one to three months in the active phase and six-monthly thereafter.

For the purpose of analysis eyes were divided into three groups – those with a normal macula (group A), those with macular pathology away from the main lesion (group B) and those with extensive exudative detachment of the retina including the macula, at presentation (group C). The follow-up ranged from 3 months to 48 months (mean follow-up 15 months).

Results

Demographic characteristics

There were 17 eyes of 16 patients who were treated for peripheral retinal vascular malformations. The age ranged from 13 years to 48 years (mean age 25.4 years). There were 14 males and 2 females in this group. The type of vascular malformation included a solitary angioma (2 eyes), Juvenile Coat's

Table 1. Clinical characteristics and treatment outcome in eyes with normal macula (group A)

Case No.	Age/sex	Initial VA	Retinal lesion	Treatment	Final VA	Final anatomy	Follow-up
# 4	15 M	20/50	Juvenile Coat's, Vit. hage	Laser	20/30	Regressed lesions	3 years
# 7	16 M	20/30	Solitary angioma RP	Cryopexy	20/30	Regressed lesions	2 years
# 8	45 M	20/30	Solitary angioma Vit. hage	Cryopexy + laser	20/20	Regressed lesions	6 months
# 13	25 M	CF 1.5 mt	Juvenile Coat's, cataract, squint amblyopia macula normal	Cryopexy	CF 1.5 mt	Regressed lesions	2 years

RP – Retinitis Pigmentosa.

disease (8 eyes), adult-onset retinal telengiectasia (5 eyes), telengiectasia with retinitis pigmentosa (1 eye), and indeterminate type (1 eye).

Clinical characteristics and treatment outcome

Group A. Eyes with normal macula, at presentation (Table 1)
There were 4 eyes seen in this group. The presenting complaint was vitreous floaters (case #8), or decreased vision in same eye (cases #7 and #13) or the fellow eye (case #4). The initial visual acuity ranged from 20/30 to 1.5 meters in these four eyes. The cause of decreased vision included mild vitreous haemorrhage with vitreous floaters in 2 eyes (cases #4 and 8), retinitis pigmentosa in one eye (case #7) and cataract with strabismus and amblyopia in one eye (case #13).

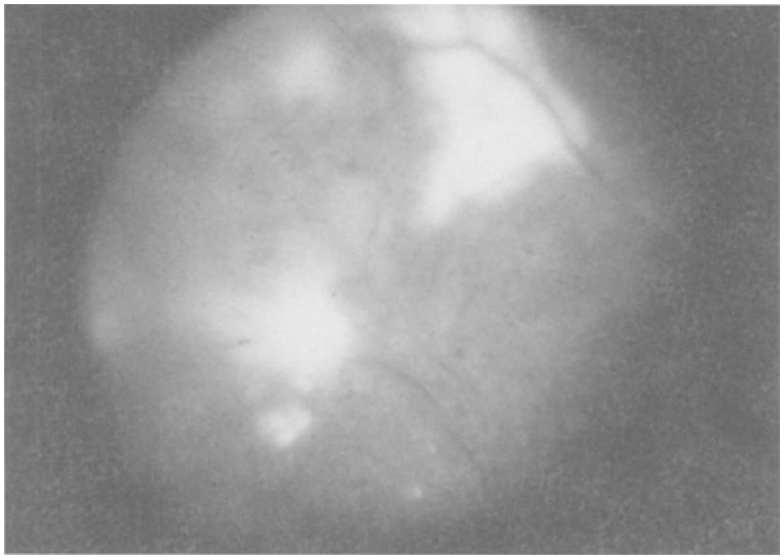
All four eyes underwent treatment with argon laser or cryotherapy or both. After treatment, visual acuity improved in two patients due to absorption of the associated vitreous haemorrhage, and remained unchanged in the other two. None of the eyes developed any complications after treatment. All four eyes were stable with regressed lesions at the last follow-up visit.

Group B. Eyes with associated macular pathology (Table 2)
There were 10 eyes in this group. The type of macular pathology included macular oedema with or without hard exudates or localized serous retinal detachment (5 eyes), epiretinal membrane (2 eyes), retinal vascular malformation encroaching onto the macula (2 eyes) and macular hole (one eye). The initial visual acuity ranged from counting fingers at one-meter to 20/70 in this group.

Table 2. Clinical characteristics and treatment outcome in eyes with macula involved (group B)

Case No.	Age/sex	Initial VA	Retinal lesion	Macular pathology	Treatment	Final VA	Final anatomy	Follow-up
# 1	13 M	CF 1 mt	Juvenile Coat's	AVM in macula	Cryopexy + laser	CF 30 cms	Partly regressed	1 year
# 2	48 M	20/70	Adult telengiectasia temporally	CME	Laser	20/80	Primary Lesion regressed. CME with HE persisting	1.5 years
# 3	30M	CF 1.5 mt	Adult telengiectasia inferiorly	HE + oedema	Cryopexy	CF 1 mt	Primary Lesion Healed. Macula status quo	2 years
# 6	15 M	CF 1 mt	Juvenile Coat's	HE + oedema	Cryopexy	CF 1.5 mt	Primary Lesion Healed. Macula status quo	2 years
# 9	20M	20/80	Juvenile Coat's	ERM	Cryopexy	20/40	Lesion Healed. ERM partially regressed with PVD	1 year
# 10	35 M	20/200	Adult telengiectasia multiple around arcades	Cellphane like ERM	Laser	20/80	Lesion Healed. ERM regressed	2 years
# 12	15 F	20/200	Angiomatosis retinae with angioma at 12 o'clock. CT normal	HE + oedema	Cryopexy	20/30	Angioma regressed. HE and oedema resolved	2 years
# 14	16 M	20/100	Juvenile Coat's	Macular hole	Laser + cryopexy	20/125	Primary Lesion Healed. Macula status quo	3 years
# 15	19 M	20/400	Juvenile Coat's	HE + oedema	Laser + cryopexy	20/100	Primary lesion regressed. HE and oedema partially resolved	2 years
# 16	45 M	20/200	Adult telengiectasia	AVM in macular area	Laser	20/200	Partially regressed	3 months

AVM — Arterio-Venous Malformation; CME – Cystoid Macular Oedema; CT – CT Scan Brain; ERM – Epiretinal Membrane; HE – Hard Exudates; PVD – Posterior Vitreous Detachment.



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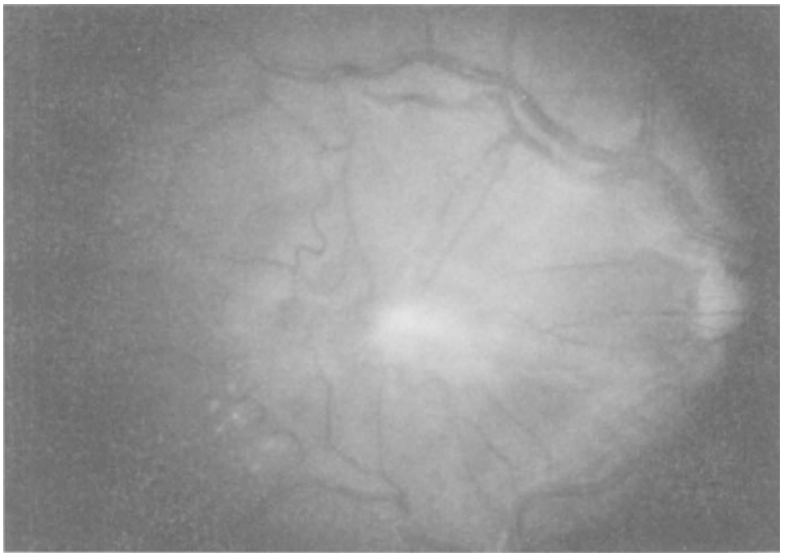

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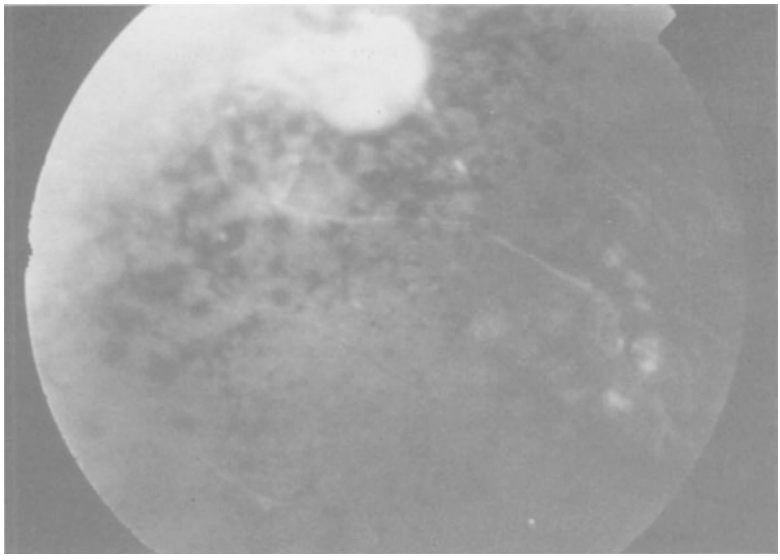
Figure 1. (a) Juvenile Coats' disease with lipid exudation in the periphery. (b) ERM in macula. VA 20/80 (case #9).



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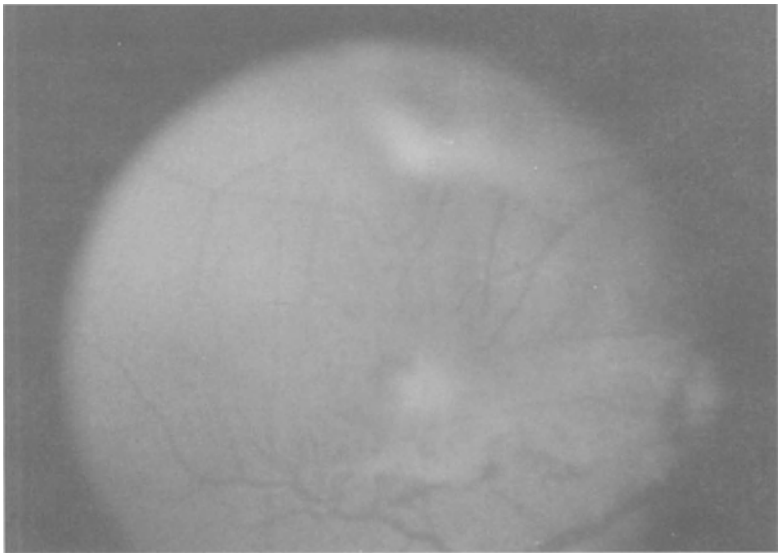

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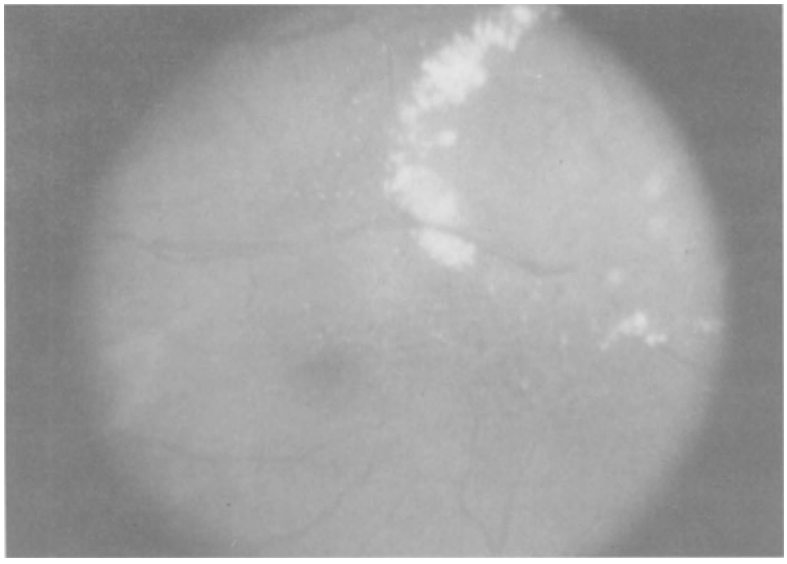
Figure 2. (a) Regressed peripheral lesion after treatment. (b) ERM partially peeled off due to PVD. VA 20/40 (case #9).



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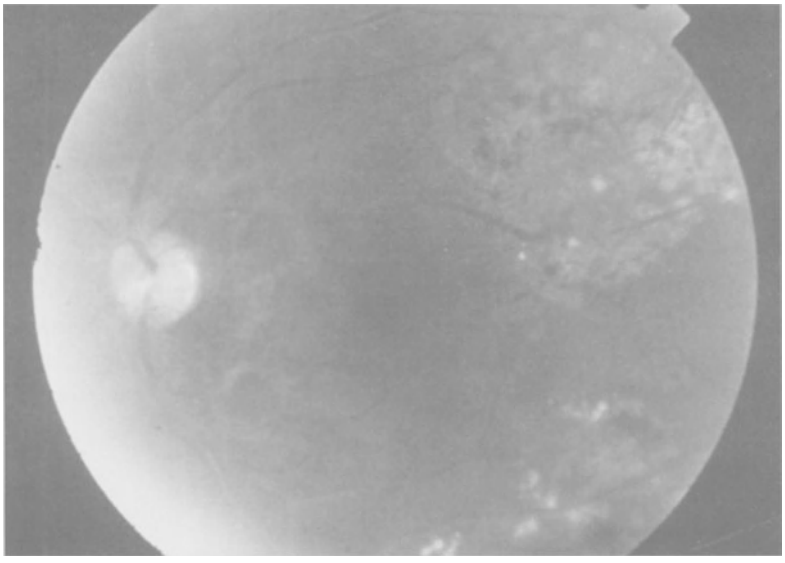


(b)

Figure 3. (a) Adult retinal telengiectasia with hard exudates around the arcades and cellophane ERM in the macula. VA 20/200. (b) Regressed lesions after laser treatment and partial regression of the macular cellophane reflex. VA 20/80 (case #10).

All eyes were treated with either cryopexy or laser photocoagulation or both. Six eyes had more than one session of treatment. At the last follow-up, visual acuity was the same, (within one line of initial visual acuity on the Snellen's chart) in 6 eyes and had increased by two or more lines in 4 eyes. Of the four eyes with increased visual acuity, two had partial spontaneous regression of the ERM after treatment (cases # 9 and 10; Figures 1a–3b), and in two eyes, the macular oedema and hard exudates had resolved (cases #12 and 16). At the last follow-up, the primary vascular lesions were stable or regressed in 8 eyes while in 2 eyes they were still active but further treatment was not done due to poor prognosis.

Group C. Eyes with extensive exudative detachment involving the macula, at presentation (Table 3)

Three eyes presented with extensive exudation and peripheral retinal vascular malformations. One of these had Juvenile Coat's disease (case #4), and one had multiple peripheral retinal angiomas (case #11). The third patient (case #5), had an indeterminate type of vascular lesions with extensive exudation, resembling Coat's disease. However, the fellow eye of this female patient was also blind with exudative detachment and so did not follow the usual description of Coat's disease as a unilateral affliction in boys. Two cases (cases #4 and 5) underwent initial cryotherapy. In one case (case #4) the visual acuity decreased rapidly over a four month period from 20/50 to PR inaccurate following increase in the exudative detachment; the other eye of this same patient with less extensive lesions and no macular involvement did well with treatment. The visual acuity and retinal pathology in case #5 remained the same over four years of follow-up and so no further surgical or cryotherapy was contemplated due to high risk of losing the residual vision which she had in her only seeing eye. One eye (case #11) underwent scleral buckling and cryotherapy to the peripheral angiomas after subretinal fluid drainage, and had partial resolution of the detachment and hard exudates (Figure 4a, b), and scarring of the angiomas three months after surgery. One year after surgery the ocular condition is same as at three months.

Overall results

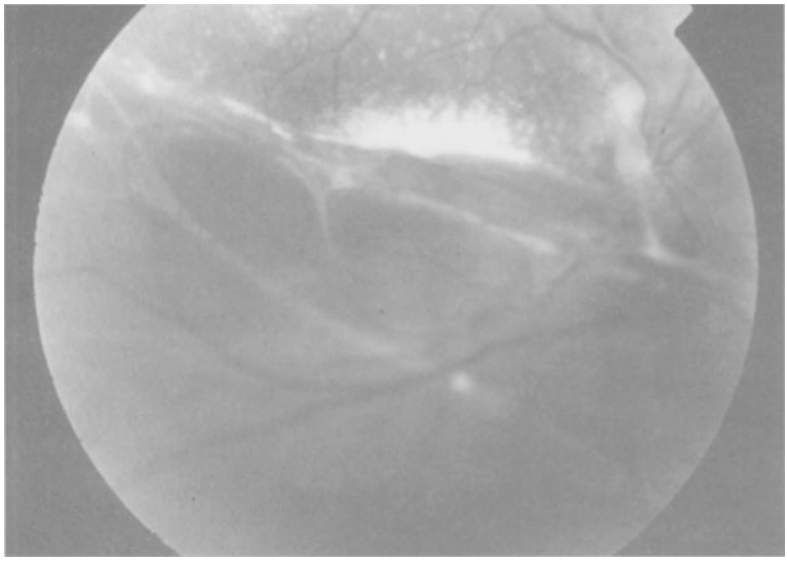
Of the 17 eyes in this series visual acuity had improved in 7 eyes, decreased in one eye and remained stable in 9 eyes at the last follow-up. A visual acuity of 20/50 or greater was seen in 5 eyes, 20/70 to 20/400 in 6 eyes and less than 20/400 in 6 eyes.

The details of clinical presentation, treatment modalities and treatment outcome are given in Tables 1–3.

Table 3. Clinical characteristics and treatment outcome in eyes with exudative detachment in macula (group C)

Case No.	Age/sex	Initial VA	Retinal lesion	Treatment	Final VA	Final anatomy	Follow-up
# 11	40 M	PL + PR accurate	Peripheral adult angiomas inferiorly. Exud. RD with HE and sub-retinal bands	Schleral buckling + fluid drainage and cryopexy	20/125	Retina attached and angiomas regressed	1 year
# 4 *	15 M	20/50	Juvenile Coat's with Exud. RD close to macula	Cryopexy	No PL after 4 months	Increased retinal detachment	3 years
# 5 **	24 F	CF 1.5 mt	Telengiectasia in periphery with Exud. RD in macula	Cryopexy	CF 1.5 mt	Peripheral lesion regressed. Macula status quo. No further treatment	2 years

*Other eye of same patient in Group A.
**Other eye had peripheral telengiectasia with total RD and no light perception.



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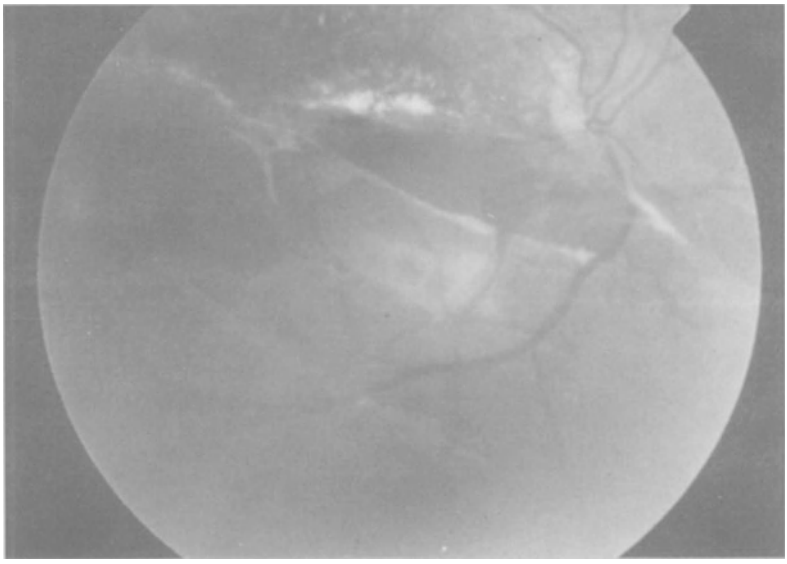

(b)

Figure 4. (a) Exudative retinal detachment, hard exudates, subretinal bands in an eye with peripheral retinal angioma. VA Light projection (case #11). (b) Attached retina and reduced hard exudates 3 months after surgery. VA 20/125 (case #11).

Discussion

Peripheral retinal vascular lesions may be asymptomatic and remain undetected, unless they cause a vitreous haemorrhage or loss of central vision due to secondary effects on the macula or progress to massive exudative retinal detachment involving the macular area. The exact incidence of macular involvement due to peripheral retinal vascular lesions is not known since the asymptomatic patients are unlikely to visit the ophthalmologist. Even small peripheral retinal angiomas can reduce vision by causing macular oedema and exudation. Although the pathogenesis of this maculopathy is unknown, there is some evidence that subtle leakage of fluid from the angioma to either the subretinal space or to the interstitial retina is responsible [3, 9, 12] with gravity playing a possible role in the accumulation of fluid [3].

The effect of treatment of the primary lesion on the maculopathy and visual acuity is not widely reported. In a series of 10 eyes, of peripheral retinal telengiectasia in adults, reported by Laqua etal [6], the macula was involved in 6 eyes and included macular pucker in 4 eyes and oedema in 2 eyes. However they did not report on the initial or final visual acuity or treatment outcome in these patients. Laatikainen et al. [11] reported the effect of therapy on macular pucker in 5 eyes with solitary peripheral retinal angiomas. The visual acuity improved after cryotherapy in one eye and after additional surgical removal of the membrane in two eyes, while it remained the same in the other two eyes.

In our series of 17 eyes the maculopathy seemed to be unrelated to the nature of the primary lesion although the primary retinal vascular pathology was variable. The three eyes in group C had extensive exudative retinal detachment involving the macular area and seemed to have more advanced pathology with poorer prognosis and so these eyes were analysed separately. Of the other 14 eyes, isolated macular involvement was seen in 10 eyes (71.4%), and was the commonest cause of visual loss. Two of the four eyes without macular pathology (group A), had only mild loss of vision due to vitreous haemorrhage which improved after treatment and regression of the primary vascular lesion. One eye in group A did not improve due to cataract, amblyopia and a squint.

In contrast, of the 10 eyes with macular pathology (group B), the presenting visual acuity was quite poor but in 4 eyes (40%), it improved after treatment and regression of the primary lesion. In 6 eyes however, the visual acuity did become stable and has remained so till the last follow-up. The two eyes with an epiretinal membrane (ERM) had partial improvement of their vision and macular pathology after treatment (Figures 2b, 3b). Spontaneous regression of the macular pucker after successful cryotherapy of a retinal angioma

was earlier reported by Schwartz et al. [9]. An ERM was seen in 5 of the 12 eyes (41%), in the series of isolated acquired retinal hemangiomas reported by Shields et al. [8]. However, in none of them was the original vascular lesion or the ERM treated by any modality as they had only mild visual loss. Details of final visual outcome were not provided.

In eyes with telengiectatic lesions close to or involving the macula, treatment seemed to stabilize the vision and prevent further loss, rather than cause any improvement. The occurence of a macular hole in one of our patient is rather rare in eyes with primary retinal vascular malformations and, to the best of our knowledge, has not been reported before except in one case of bilateral macular holes in a patient with Von Hippel–Lindau disease [13].

Eyes with macular edema with or without hard exudates, had a variable outcome. Two of the 5 eyes (40%) showed a remarkable recovery after treatment and the other three having no further visual loss. The numbers in our series are too small to ascertain the various factors which could influence visual outcome in eyes with macular oedema and hard exudates, but possible factors include the age of the patients, duration of the macular pathology and its extent. In the series of 5 patients by Campochiaro et al. [14], macular edema was present in 3 eyes. After cryopexy/laser of the original vascular lesion, vision improved in one eye, deteriorated in two eyes and was stabilised in one eye.

As expected, the eyes in group C had the worst visual outcome. One of the eyes rapidly lost vision after cryotherapy due to further extension of the exudative detachment. It is difficult to ascertain whether this was solely due to the treatment, as the deterioration started from 4 months after the treatment till loss of light perception 8 months later. Conversely, it may have been due to the natural course of advanced retinal telengiectasia with exudative retinal detachment. Loss of vision following cryotherapy, resulting in increased exudative detachment in an eye with 20/20 vision and no macular pathology has been mentioned by Gass [15]. One patient in this group had a retinal detachment of the inferior two quadrants with angiomas inferiorly and was treated with scleral buckling and cryotherapy. After three months of follow-up he had improvement in visual acuity which has remained so at one year of follow-up.

In conclusion, we wish to highlight the response to treatment of the primary retinal vascular lesion(s), in eyes with and without macular pathology. In eyes without macular pathology, response to treatment was good, with visual recovery and regression of the primary lesions. In eyes with macular pathology, those with macular puckers and macular oedema had a more favourable outcome than eyes with primary lesions close to or involving the macular

area. Eyes with extensive exudation may not be amenable to any therapy and the few eyes where treatment may be attempted, could have a fair outcome.

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The pathogenesis and clinical presentation of macular edema in inflammatory diseases

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Abstract. Cystoid macular edema (CME) is a classical complication of ocular inflammation. This syndrome was already described by Irvine in 1953 but the pathogenesis of this condition remains unclear. Cystoid macular edema can result either from a rupture of the inner or from the outer blood ocular barrier. Clinical CME that is responsitble for a low visual acuity must be differentiated from angiographic CME that can be present even without any decrease in visual acuity. Fluid progressively accumulates into the outer plexiform layer of the retina and pools into cystic spaces. Fluid accumulation can now be better seen with optical coherence tomography (OCT). In chronic CME fluid accumulation is associated with thinning of the retina and fibrosis. At this stage irreversible lesions are present and CME does not respond to medical therapies. Inflammatory CME must be differentiated from CME resulting from irreversible vascular damage such as in diabetic CME or due to vein occlusions. Experimental research on cystoid macular edema has been hampered by the lack of animal model: most of laboratory animals have no macula, monkeys appear to be highly resistent to macular edema. Five major causes have been suspected to be at the origin of CME: (1) photic retinopathy, (2) trauma of ocular tissue, (3) secondary irritation of the ciliary body, (4) vitreous traction and (5) pharmaceutically induced CME. Clincial experience has shown that pseudophakic CME usually responds well to local therapy of steroids and non-steroidal antiinflammatory drugs (NSAIDs) and/or in association with systemic acetazolamide. Acetazolamide is increasing fluid resorption through the retinal pigment epithelium. Postoperative CME rarely needs additional posterior subtenon's injections to resolve. But in CME occurring secondary to uveitis additional posterior sub-Tenon's steroid injections or systemic steroids may be necessary to decrease the constant release of inflammatory mediators.

Key words: cystoid macular edema, cytokines, inflammation, pathogenesis, prostaglandins

Introduction

Cystoid macular edema is a common cause of decrease of visual acuity occurring in many ophthalmic diseases. It can either result from a rupture of the inner or outer blood-ocular barrier. In inflammatory diseases vascular exsudation in the macular region results from a transient increase in vascular permeability. The mechanism of onset of cystoid macular edema in inflammatory diseases differs from the pathogenesis of cystoid macular edema in venous obstruction where an increase in intravascular pressure is described

[3]. In diabetes mellitus, irreversible lesions of capillaries are present, a decrease in capillaries pericytes has been observed [4]. There are two main conditions responsible for macular edema in ocular inflammation: surgical trauma or endogenous uveitis. In each of these conditions, the inflammatory cascade is switched on, and the same inflammatory mediators are secreted. But the process differs from the intensity and the duration of the triggering factors.

Irvine was the first in 1953 who mentioned macroscopic changes of the macula with a loss of the foveolar reflect: the decrease of visual acuity was associated with a prolapse of the vitreous into the anterior chamber of the eye after uneventful intracapsular cataract extraction [1]. Macular thickening results due to the accumulation of fluid within the retina and leakage of fluorescein appears in the early stages of angiography developing into a petaloid pattern in the late stages [2]. But fluorescein angiography leakage can be seen in some patients even in the absence of a decrease of visual acuity. For this reason angiographic cystoid macular edema must be differentiated from clinical cystoid macular edema. Histologic sections have shown a typical cystoid pattern within the outer plexiform Henle layer. These images suggest that a serious exsudation from the intraretinal capillaries in the macular region could be at the origin of visual disturbance. Restoration of vascular permeability occurs after resolution of cystoid macular edema. But after prolonged macular edema degenerative changes occur with retinal thinning and progressive fibrosis [2].

In inflammatory cystoid macular edema, the good clinical response observed after therapy with either systemic steroid therapy or posterior sub-Tenon's steroid injections suggests that a reversible process is induced by ocular inflammation.

The inflammatory cascade

Inflammatory mediators are secreted inside the eye during surgery or autoimmune uvetis. The inflammatory cascade is a mechanism of defense that the immune system of vertebrates has developed against the invader. Several more or less archaic pathways of defense have been selected during the evolution. The same pathways of defense can be triggered by various stimuli. The response of the immune system is proportional to the degree of stimulation (local response, systemic disease, shock...).

The arachidonic acid pathway is one example that has been widely investigated in inflammatory macular edema. Clinical studies have shown the protective role of NSAIDs against the onset of cystoid macular edema after surgery [5, 6]. NSAIDs have also an effect on ocular mydriasis during sur-

gery. Therapeutic effect of NSAIDs on cystoid macular edema still remains to be proven but has been suspected by many authors.

Many other inflammatory mediators such as cytokines are also involved in the onset of cystoid macular edema. Inflammatory cytokines are small peptides that are regulating inflammation. Proinflammatory cytokines such as TNFα and IL-1β have been suspected to induce a rupture of the blood-ocular barrier [7]. TNFα and IL-1β induce a secondary intraocular chemokine production. We have recently shown that CINC, an interleukine-8 analogue in rats, is produced inside the eye and was responsible for polymorphonuclear chemotactism. Inflammatory cells themselves (when they are at the site of inflammation) can also induce a secondary production of cytokines and mediators that have an effect on the blood-retinal barrier. Intraocular proinflammatory cytokine injection can e.g. induce a breakdown of the blood-aqueous barrier [8].

High levels of proinflammatory cytokines have been measured in AIDS patients, and the imbalance of proinflammatory cytokine production could be one of the mechanism involved in cystoid macular edema occurring in AIDS patients under HAART (highly active antiretroviral therapy).

Many vasoactive peptides such as bradykinines or kallikreines are probably also involved in the onset of a breakdown of the blood-retinal barrier. Further clinical and experimental data should be collected to help in the understanding of macular edema.

The blood-retinal barrier, pigment epithelium and vascular endothelium

The three following anatomical structures are forming the junctional complex responsible for the blood-retinal barrier of the pigmentary epithelium: the tight junctions or *Zonulae occludens*, *Zonulae adherens* and *Macula adherens*. [9]. *Zonulae occludentes* that are also present between vascular endothelial cells of the retina prevent the movement of macromolecules towards the interstitium [10]. The integrity of the endothelial cells, pigment epithelial and zonulae occludentes are at the origin of the blood-retinal barrier. This functional entity maitains the constancy of the environment of ocular neurons and photoreceptors. The retinal pigment epithelium is not only a barrier but it is also responsible for active transport of fluids from the vitreous cavity to the choroid [11]. Carbonic anhydrase enzymes which are attached to the cell membrane of pigment epithelial cells are involved in this process. This powerful pump mechanism is able to evacuate large amounts of fluids from the retina; the process can be increased by carbonic anhydrase inhibitors [12, 13] with a consecutive increase in visual acuity [12]. Carbonic anhydrase

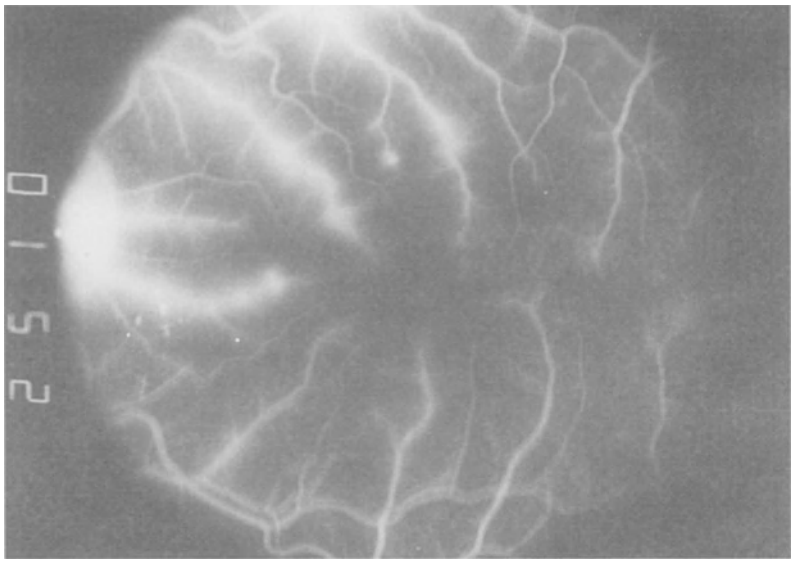


Figure 1. Severe perimacular vasculitis in experimental autoimmune uveitis in cynomolgus monkeys. Inflammation occurs about 2–3 weeks after immunization of the monkeys with recombinant S-Antigen. Despite severe vasculitis no typical petaloid pattern of cystoid macular edema can be seen during fluorescein angiography.

inhibitors were also helpful in reducing macular edema in retinitis pigmentosa [14, 15].

Animal models of ocular inflammation and cystoid macular edema

Most animals used in laboratory experiments to study ocular inflammation such as rats and mice have no macula. Therefore, non human primates have been previously used to study macular edema [16]. Cataract extraction was, e.g. performed in monkeys by Tso and coworkers to induce cystoid macular edema. However, none of the animals developed the typical angiographic petaloid pattern of cystoid macular edema. Histologic analysis of these eyes showed horseradish peroxydase tracer leakage through both the retinal pigment epithelium and the retinal vessel walls. These data are highly suggestive of a breakdown of the inner and outer blood retinal barrier [16]. Photic maculopathy could be produced after exposition of monkeys to the light of an indirect ophthalmoscope [16]. A focal leakage of fluorescein was present but none of the animals had a typical petaloid pattern of leakage.

Severe uveitis is also frequently associated with cystoid macular edema. Experimental autoimmune uveitis is an animal model of posterior pole inflammation that mimics sympathetic ophthalmia. Animals are immunized

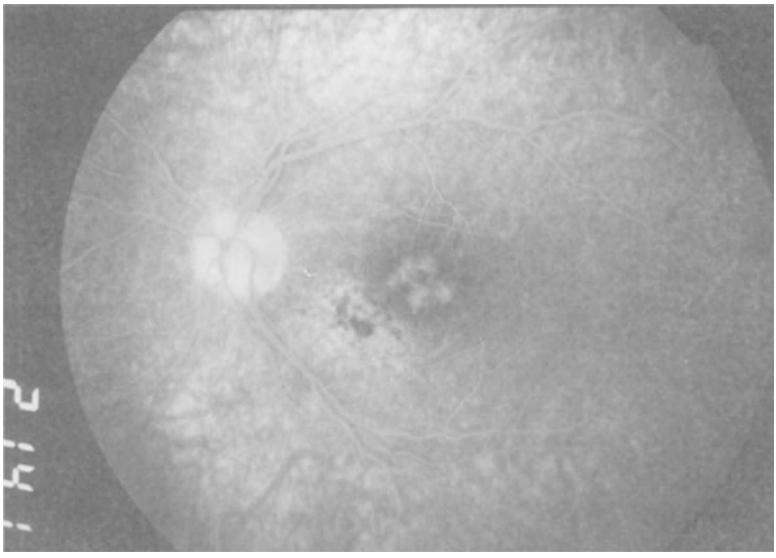
with incomplete Freund's adjuvant and S-antigen or interphotoreceptor binding protein (IRBP) [17–20]. The disease occurs about 2 to 3 weeks after immunization. In order to test the antiinflammatory effect of a humanized antibody that blocks the α-chain of the interleukin-2 receptor during 3 different experiments 35 cynomolgus monkeys were used [21]. Disease evolution was followed every two weeks by fundoscopy and a fluorescein angiography was performed at the beginning of ocular inflammation. All animals developed a severe ocular inflammation with perivascular sheathing. Fluorescein angiography showed leakage but none of the animals presented typical petaloid pattern during angiography (Figure 1) [21].

In summary, cystoid macular edema with a typical petaloid pattern cannot be easily induced in monkeys or in other animal models. The knowledge of the mechanisms of inflammatory macular edema has thus mainly come from clinical studies.

Ocular inflammation in surgery and photic maculopathy

Surgical intraocular procedures are responsible for a transient increase in ocular inflammation. The rupture of the blood-aqueous barrier, reflecting the level of ocular inflammation, has been measured by laser flare photometry [22, 23], and, in terms of therapy, a protective effect of NSAIDs or topical steroid on ocular inflammation has been clearly demonstrated [23]. In pseudophakic CME the following pathophysiological mechanisms have been implicated: (1) photic retinopathy; (2) trauma of ocular tissues; (3) secondary irritation of the iris or ciliary body by the lens; (4) vitreous traction; (5) pharmacologically induced CME.

1. Phototraumatism of the retinal pigment epithelium is a frequent cause of CME after cataract surgery. Three mechanisms can be involved in light damage: (a) thermal, (b) mechanical and (c) photochemical. Thermal lesions result from light absorption by the retinal pigment epithelium. Mechanical light damage appears with the use of the Q-switched mode with neodymium-ytrium-aluminium-gardnet (ND-YAG) laser. Photochemical damage occurs through the operating microscope after a prolonged operating time [16, 25, 26]. The exact mechanism is still unknown but the light produces lesions at the level of the outer segment of the photoreceptors. Tissue oxidation by prolonged light exposure is probably also implicated. The retinal lesion appears as a light yellow to white oval area with a parafoveolar location (Figure 2). Fluorecein leakage is present in the early stage and can be seen at the level of the lesion. Photic maculopathies have been suspected to be at the origin of cystoid macular edema [27–29].



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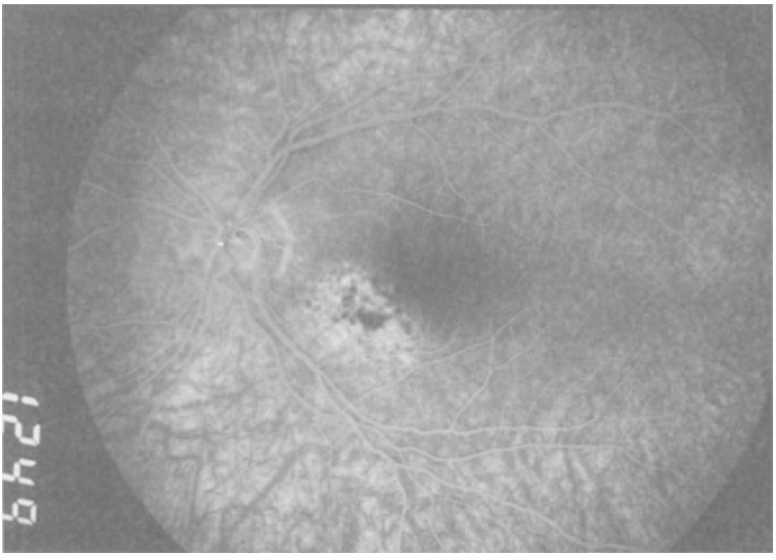

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Figure 2. Typical photic maculopathy associated with macular edema in a patient after lens fixation to the sulcus. No clinical response was seen after therapy with slow released acetazolamide 500 mg/day associated with topical application of diclofenac sodium 0.1% drops TID and prednisolone acetate drops TID. A clear decrease of macular edema was seen after a series of three additional posterior sub-Tenon's steroid injections that were given at three weeks intervals. But a perimacular scar secondary to photic maculopathy is still present.

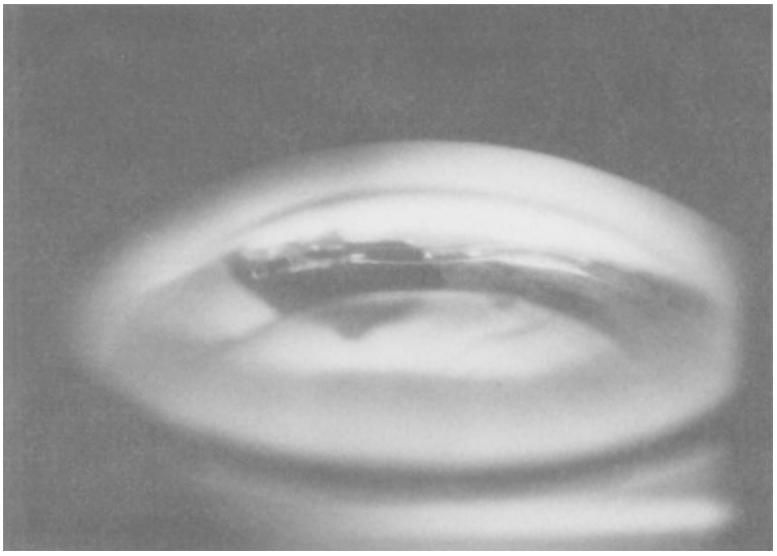
2. The iris is a very susceptible tissue that can liberate secondary inflammatory mediators after surgical manipulation. During surgery the triggering factor (surgical trauma) is transient. Once the noxious stimulus has stopped, the healing process is sufficient to progressively taper down the inflammation. After extracapsular cataract extraction a spontaneous resolution of cystoid macular edema is seen, after one year in 14/18 (78%) macular edema are healed and in 17/18 eyes (94%) within two years [30]. In pseudophakic eyes with an iris fixated lens the outcome is less favorable with only 44% of spontaneous resolution [31]. Lens fixation to the sulcus is also associated with a high risk of macular edema. Photic maculopathy is a classical complication seen after lens fixation to the sulcus.

But constant mechanical irritation of the sulcus is probably another factor favoring the onset of macular edema. Such irritation of the ciliary body can be seen when the haptic of anterior chamber lens is is touching the ciliary body through the iridectomy (Figure 3). The mechanical irritation of the ciliary body is also classically involved in the onset of postoperative cystoid macular edema. Reposition of anterior chamber lens is necessary when the haptic of the lens is touching the ciliary body through the peripheral basal iridectiomy.

The prophylactic use of prostaglandins inhibitors in the cataract surgery prevents the onset of CME after cataract extraction [5, 6, 32–35]. In a prospective study we used a two step approach for the treatment of inflammatory cystoid macular edema. The first line of therapy consisted of diclofenac 0.1% eye drops TID associated with prednisolone acetate TID and systemic administration of sustained released acetazolamide 500 mg daily. In this study, 11/25 eyes presented a cystoid macular edema after cataract surgery. Seven of them had a good clinical response to the therapy: mean visual acuity (measured with Snellen Chart) increased from 0.31 ± 0.13 to 0.93 ± 0.08 ($p \leq 0.001$) after three weeks of therapy. All therapy could be removed after a mean time of 4 months and none of them presented a clinical relapse of CME. The mean follow-up without therapy was of 10 ± 3 months [24]. This clinical approach of cystoid macular edema suggest that macular edema induced by cataract surgery can be managed by systemic acetazolamide and topical anti-inflammatory therapy. Spontaneous resolution of macular edema have been observed but our patients had a good visual acuity already after a 3 weeks therapy.

Ocular inflammation in endogenous uveitis

Contrary to surgical trauma, endogenous uveitis produces a constant release of inflammatory mediators. The natural course of inflammatory CME in uveitis is thus not a self limited disease leading to spontaneous resolution.



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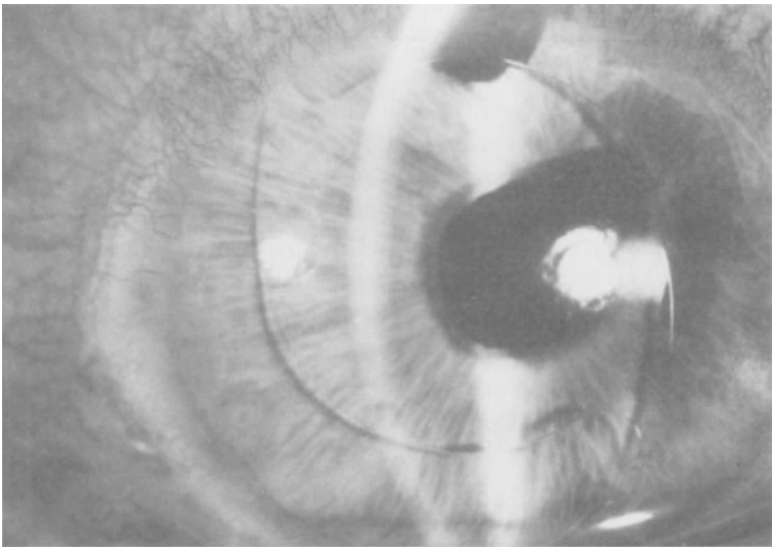


(b)

Figure 3. (a) The haptic of an anterior chamber lens is passing through the iridectomy. (b) Gonioscopic view of the haptic of an anterior chamber lens that is touching the ciliary body. This mechanical irritation is responsible for a secondary macular edema. Rotation of the lens is necessary to avoid the chronic irritation by the haptic of the ciliary body.

Without any therapy a chronic evolution of CME is the rule with a progressive thinning of the macula. In the late stages a fibrosis of the macula can be seen with irreversible macular changes. In these advanced stages of the disease no therapy may be sufficient to restore good visual acuity.

Uveitis is classified according to the anatomical localisation of ocular inflammation. In acute anterior uveitis inflammation is mostly limited to the anterior segment of the eye and cystoid macular edema is decribed in about 30% of the patients of HLA-B27 positive patients as compared to 8% of HLA-B27 negative patients [36, 37]. In acute anterior uveitis cystoid macular edema should thus be systematically looked for in the presence of a decrease in visual acuity occurring several weeks after the acute onset of uveitis. In intermediate and posterior uveitis cystoid macular edema is more frequently seen.

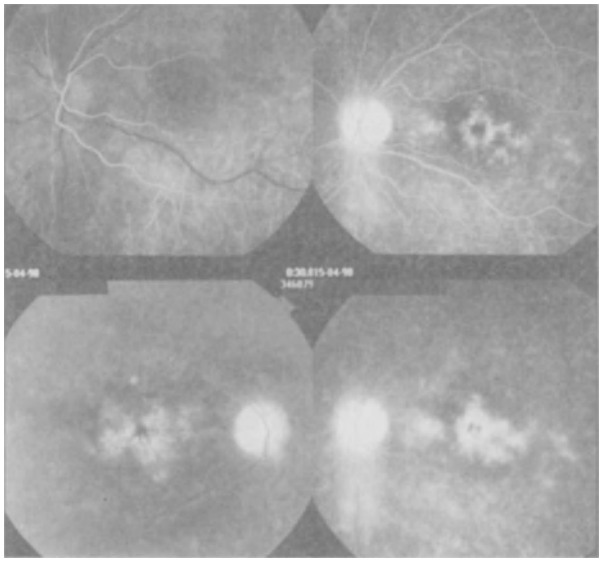
Macular edema associated with Highly Active Antiretroviral Therapy (HAART)

The recent introduction of a highly active antiviral therapy (HAART) associating two reverse transcriptase inhibitors with one protease inhibitor has changed the follow-up of Cytomegalovirus (CMV) retinitis in HIV patients. When an HAART is introduced an increase in CD4+ cells is seen with a decrease in the patient's HIV viremia. In some patients the anti-Cytomegaloviral therapy could be cancelled without relapse of cytomegalovirus retinitis. These patients present a better immune response which can inhibit retinal CMV infection without the adjunct of ocular antivrial therapy (Figure 4a and 4b).

Parallel to the increase in CD4+ cells, some patients have developed CME and it has been argued that the increased immune response is responsible for this.

Conclusion

The pathogenesis of cystoid macular edema in inflammatory disorders is made up of several inflammatory mediators which are released in the course of the disease. In contrast to postoperative inflammation, where the noxious influence is of limited duration, the release of inflammatory mediators in the course of an uveitis is more chronic which will invariably perpetuate the retinal damage. In the therapy of inflammatory cystoid macular edema, a combined approach is useful. The acetazolamide is helpful to increase the resolution of fluid through the retinal pigment epithelium. Topical application of NSAIDs are probably useful but their efficacy as therapeutic agent still remains to be proven. When oral administration of acetazolamide associated



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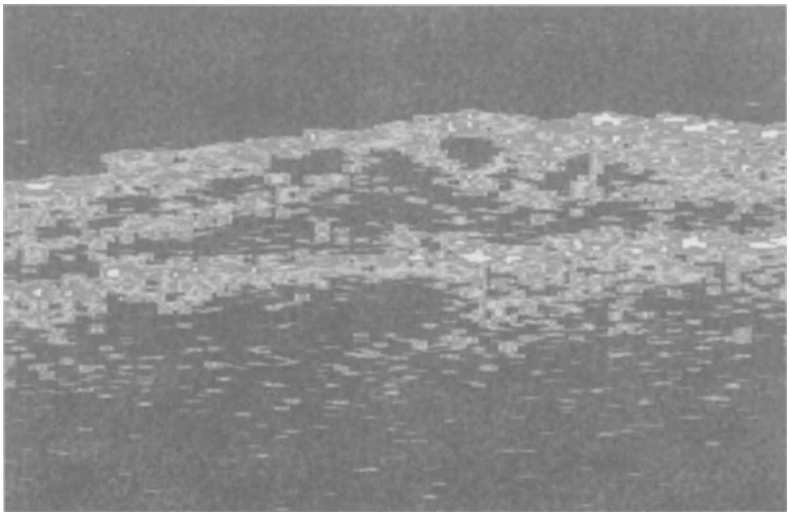

(b)

Figure 4. (a) Severe cystoid macular edema occurring in a HIV positive patient under Highly Active Antiretroviral Therapy (HAART). Macular edema occurred after increase of CD4+ cells and healing of cytomegalovirus retinitis. (b) Typical cystoid pattern is visible on optical coherence tomography (OCT) images.

with topical application of NSAIDs and steroids are not sufficient, posterior subTenon's steroid injections systemic steroids may be indicated [38, 39].

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Cystoid macular edema in a patient with acquired immunodeficiency syndrome and past ocular history of cytomegalovirus retinitis after initiation of protease inhibitors

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Abstract. *Purpose:* To describe a patient with acquired immunodeficiency syndrome (AIDS) who presented with cystoid macular edema (CME) which was not associated with active cytomegalovirus (CMV) retinitis or AIDS-related microvasculopathy. *Method:* A 32-year-old man with AIDS and a past ocular history of inactive CMV retinitis was placed on protease inhibitors when his $CD4^+$ T lymphocyte counts dropped to 8 cells/mm^3. Three months later, after his $CD4^+$ T lymphocyte counts had increased to 196 cells/mm^3 he complained of micropsia and metamorphopsia in his right eye of 1 week duration. The patient had a complete ocular examination including fluorescein angiography (FA). *Results:* Visual acuity (VA) was 7/10 OD. Fundus examination revealed CME and inactive CMV retinitis, and FA demonstrated CME and a hot disc. Two transseptal injections of corticosteroids were administered 2 weeks apart in the right eye as treatment of the CME. The patient reported gradual visual improvement and 6 weeks later, his VA was $10/10^{-2}$. CME had resolved clinically and angiographically. *Conclusions:* CME in our case is associated with inactive CMV retinitis and gradually increasing number of $CD4^+$ T lymphocytes after initiation of treatment with protease inhibitors. It may be amenable to regional administration of corticosteroids without reactivation of retinitis.

Introduction

Cytomegalovirus (CMV) retinitis is the most common ocular opportunistic infection in patients with the acquired immunodeficiency syndrome (AIDS) [1]. It is typically characterized by necrotizing retinitis and vasculitis with little or no intraocular inflammatory response. CMV retinitis in patients with AIDS is associated with $CD4^+$ T lymphocyte counts below 100 cells/mm^3 [1,2] (usually <50 cells/mm^3)[1,2]. The immune status, as indicated by the levels of $CD4^+$ T lymphocytes and the levels of plasma HIV messenger-RNA [3] has been improved in many AIDS patients after the introduction of HIV-specific protease inhibitors.

Palestine and Frishberg [4] reported a patient with AIDS-related macular edema with cotton-wool spots, other microvascular abnormalities, and, eventually, a macular star, which was attributed to HIV microvasculopathic complications. A patient with CME associated with AIDS and CMV retinitis was described by Weinberg and Moorthy [5]. More recently, Karavellas and coworkers described a new syndrome of posterior segment intraocular inflammation that causes visual loss in patients with AIDS and inactive CMV retinitis after initiation of treatment with protease inhibitors [6]. We evaluated a patient undergoing treatment with protease inhibitors who had rising CD4+ T lymphocyte counts and inactive CMV retinitis.

Case report

A 32-year-old homosexual man was referred to our hospital in May 1996 because of floaters and redness in his right eye. The patient was diagnosed as having AIDS, when he developed Pneumocystis carinii pneumonia, 30 months after being diagnosed as having HIV infection. His medical history was remarkable for diabetes mellitus and idiopathic thrombocytopenic purpura of 2 years' duration. On ocular evaluation his best corrected visual acuity was 10/10 in both eyes. Slit-lamp examination of the anterior segment was normal in both eyes. Fundoscopic examination of the right eye revealed peripheral retinal necrosis and vasculitis of the inferior temporal retinal quadrant, signs consistent with acute CMV retinitis. Fundus of the left eye was normal. The patient was taking azitothymidine (AZT), 3TC, in addition to rifamputin and gancyclovir as a prophylaxis for atypical mycobacteria and CMV infection respectively. The $CD4^+$ T lymphocyte count was less than 8 cells/mm^3. A diagnosis of CMV retinitis was made and the patient was immediately started with an induction dose of gancyclovir (5 mg/kg IV twice daily) for 2 weeks followed by maintenance therapy (5 mg/kg/day). Four weeks after initiation of treatment, regression of retinitis was noted. Two months later the $CD4^+$ T lymphocyte count had increased to 50 cells/mm^3. The patient was stable between August 1996 and April 1997. However, in April 1997, on a scheduled follow-up examination, progression of retinal atrophy and hemorrhages were noted. A diagnosis of chronic smoldering CMV retinitis was made and the patient was placed on induction dose of cidofovir. After one dose of cidofovir this medication was, however, discontinued due to significant reduction of platelets (<30 cells/mm^3). The treatment was then switched to foscarnet and protease inhibitors (indinavir) were added to the therapeutic regimen. The $CD4^+$ T lymphocyte counts had dropped to 12 cells/mm^3 again. Disease progression appeared to be halted for 3 months and the $CD4^+$ T lymphocyte counts had again increased to 53 cells/mm^3.

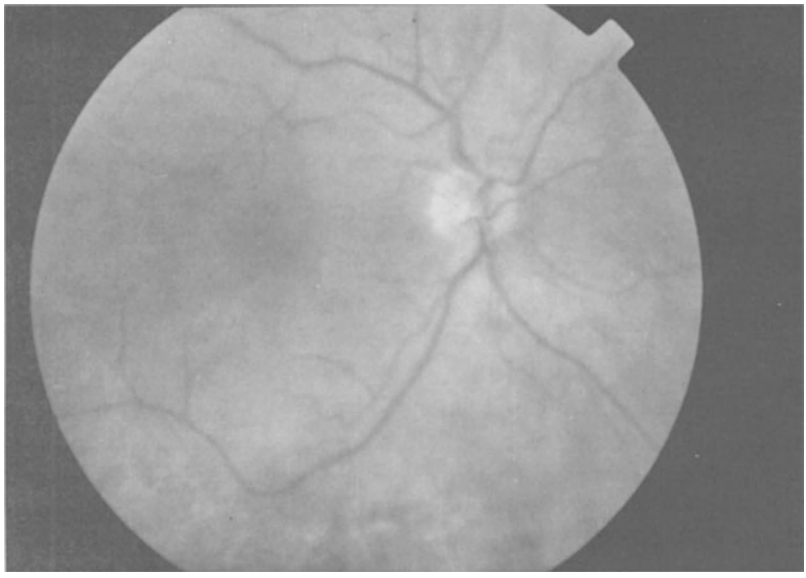

Figure 1. Fundus picture of the right eye demonstrating inactive CMV retinitis inferotemporally and cystoid macular edema.

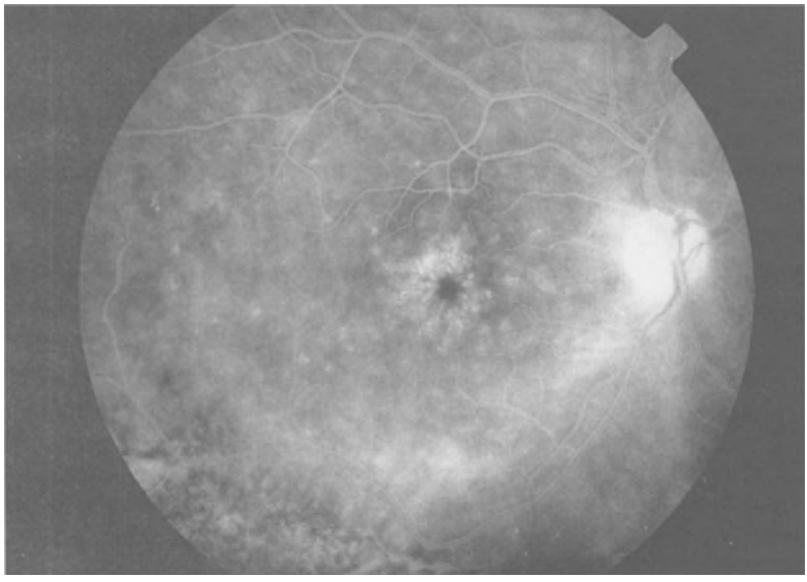

Figure 2. Late frame of fluorescein angiogram of the same eye showing optic disc leakage and multiple round and oval hyperfluorescent structures arranged in a petaloid pattern in the macula. Note the staining of the peripheral retinitis outside the inferotemporal arcade.

In October 1997, however, the patient started to complain of visual reduction, accompanied by micropsia and metamorphopsia in his right eye of one week duration, despite the fact that the $CD4^+$ T lymphocyte counts had further increased to 196 cells/mm^3 and the PCR in the blood was negative for CMV detection. Visual acuity was 7/10 OD and 10/10 OS. Fundoscopic examination was remarkable for CME in OD with no signs of recurrent CMV retinitis (Figure 1). The left eye was healthy. Fluorescein angiography confirmed the presence of CME and disc leakage in OD (Figure 2).

A transeptal injection of repository methyl-prednisolone (40 mg) was administered on October, 1997, and the patient continued maintenance therapy with foscarnet. One month later, patient's VA had improved to 9/10, but the patient was still complaining of metamorphopsia in OD. New funduscopic examination showed the persistence of CME and development of an epiretinal membrane. Another transeptal injection was given 4 weeks later and resulted in further improvement of his VA. Visual acuity improved to $10/10^{-2}$ OD.

Discussion

CMV retinitis is the most common ocular opportunistic infection among patients with AIDS [1]. The most common vision-threatening ophthalmic complications of CMV retinitis include retinitis involving the macula or optic nerve, rhegmatogenous retinal detachment, and less frequently, serous macular detachment. However, the routine use of increasingly intensive antiretroviral therapies has resulted in a dramatic decline in morbidity and mortality among HIV-infected patients with advanced immune depletion [8].

CME in patients with AIDS is rare and has been associated with AIDS microvasculopathy [4] or active CMV retinitis involving the optic disc, macula or paramacular area [5]. This is not the case in our patient. Intraocular inflammation in AIDS has also been attributed to concomitant treatment with rifamputin or cidofovir [7]. Our patient took only one dose of cidofovir and afterwards it was discontinued due to a significant reduction in platelet counts. Additionally, the dose of rifamputin had been decreased because of adverse interactions with protease inhibitors. CME could also be attributed to diabetes mellitus, but the presence of a hot disc on FA renders such a diagnosis very unlikely.

CME in our patient was associated with the presence of inactive CMV retinitis that had not caused visual loss during its active stage, combination antiretroviral therapy with protease inhibitors, and evidence of at least partial immune reconstitution suggested by elevated $CD4^+$ T cell counts. Additionally, our patient did no have symptomatic vitritis during the presence of CME.

However, CME in Karavellas and colleagues study [6] was associated with symptomatic vitritis and papillitis.

The pathogenesis of CME we described is unclear. It is possible that protease inhibitors could directly mediate this inflammation, or CME could be in response to CMV antigens expressed on cells that have been latently infected, near the areas of previously active CMV retinitis. This type of CME may be reversible with corticosteroid treatment without reactivation of CMV retinitis. Further studies are necessary to elucidate the pathogenesis of this newly described cause of CME.

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Is scleral fixation a safe procedure for intraocular lens implantation?

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Abstract. *Purpose:* No consensus currently exists on the optimal method for intraocular (IOL) implantation without capsular support. We evaluated the outcome and angiographic findings of eyes that underwent the implantation of scleral fixated IOLs. *Methods:* Iris and retinal fluorescein angiography were performed in 13 eyes that had received posterior chamber IOL implantation with scleral fixation. Follow-up examinations also assessed visual acuity (VA), intraocular pressure (IOP), IOL decentration and complications related to the procedure. *Results:* Mean visual acuity was 0.29 preoperatively and 0.71 postoperatively after a mean follow-up of 14.2 months. A best corrected visual acuity of 0.5 or better was obtained in 12 eyes. Iris fluorescein angiography did not show major vascular abnormalities. Retinal angiography showed 5 cases of macular edema. In 6 eyes light-induced retinal lesions occurred. Cellophane maculopathy was disclosed in 4 eyes. Macular edema was associated with photic injury in 4 cases and with cellophane maculopathy in 2 cases. Mean postoperative visual acuity was 0.6 in eyes with macular edema and 0.88 in eyes without (SD 0.18; range 0.5–1.0). Four of 5 eyes with macular edema had a postoperative visual acuity of 0.5 or better. There was no evidence of persistent IOP elevation or IOL decentration. No serious complications were recorded during surgery. *Conclusions:* Transscleral fixation of posterior chamber IOLs provides adequate visual acuity in most patients. Macular edema was frequently associated with the procedure. Although this complication was a cause of low visual recovery after implantation, the majority of eyes with macular edema achieved a visual acuity of 0.5 or better. Light-induced retinal injury was a permanent complication.

Key words: cellophane maculopathy, light-induced retinopathy, macular edema, scleral fixation

Introduction

No consensus exists on the ideal method for IOL fixation without capsular support. In 1986 Malbran et al. described a method for scleral fixation of posterior chamber lenses in aphakic eyes [1]. The current indications for this procedure includes large ruptures of the posterior capsule during cataract surgery or secondary implantation after a previous intracapsular procedure. In summary, three techniques for IOL fixation can be applied: (1) implantation of an anterior chamber IOL in the angle, (2) iris fixation of a posterior chamber IOL, (3) transscleral fixation of a posterior chamber IOL.

We reviewed the functional results, complications and iris and retinal angiographic findings in eyes that underwent posterior chamber lens implantation with scleral fixation.

Subjects and methods

Posterior chamber IOL implantation using scleral fixation was performed in 13 eyes. Follow-up ranged from 6 to 26 months (mean 14.2 ± 7.8 months). Posterior chamber lens implantation was performed in 2 aphakic patients after intracapsular cataract extraction; in 10 patients scleral IOL fixation was done after a capsular rupture during extracapsular cataract extraction. One patient was operated on for a retained lens nucleus and a dislocated IOL into the vitreous after phacoemulsification. In this latter case, a three port pars plana vitrectomy was performed and the nucleus as well as the IOL were removed prior to scleral fixation of a new IOL. In all the other cases an extensive anterior vitrectomy was performed.

One or two half-thickness small fornix-based scleral flaps were prepared in the desired o'clock-hour position. The needle of a 30 cm double-armed 10-0 polypropilene suture was inserted with an outside-inside technique in the bed of the scleral flap through the sclera 1 mm posterior to the limbus, through the ciliary sulcus, behind the iris, through the pupil. When two scleral flaps were prepared, a 27 gauge needle was inserted in the bed of the opposite scleral flap and advanced behind the iris. The polypropilene suture was threaded into the needle and both were withdrawn. In the case of only one scleral flap, the needle was threaded into the cornea through the limbus at the opposite site. A Sinskey hook was introduced into the anterior chamber and the suture hooked through the pupil and pulled from the anterior chamber through a corneo-scleral incision. The suture was severed outside the anterior chamber. One or two of the ends were tied to the IOL's haptic. The IOL was inserted into the posterior chamber with McPherson forceps and pulling the suture. The suture threads were fixated at the sclera under the flaps. The sclero-corneal incision was closed with a 10.0 nylon continuous suture and the scleral flaps with 8.0 silk.

All postoperative examinations and clinical reporting were performed by one (P.L.) of the operating surgeons (P.L., U.M.). Follow-up examinations measured visual acuity with Snellen acuity charts, intraocular pressure (IOP), IOL decentration recorded with the pupil in mild mydriasis. Iris and retinal fluorescein angiogram were performed three months after surgery and then every three months to detect blood-ocular barrier abnormalities or the presence of macular edema.

Table 1. Patient profiles, results and complications of transcleral IOL fixation

Case No./ Age,y/Sex	Indications for scleral fixation	Visual acuity		Angiographic ME	Angiographic iridopathy	Light-induced retinopathy	Cellophane maculopathy	Follow-up mo
		Preoperative	Postoperative					
1/82/F	Aphakia	1.00	1.00	–	PB	+	–	24
2/70/M	Aphakia	1.00	1.00	–	–	–	–	26
3/64/M	Retained nucleus	0.01	0.9	–	–	–	–	17
4/85/F	Cataract	0.32	0.6	+	PB/mS	+	–	25
5/82/M	Cataract	0.2	0.7	+	PB	+	–	19
6/79/M	Cataract	0.2	0.4	+□	–	+	+	10
7/85/M	Cataract	0.2	0.5	–	–	+	+	9
8/80/M	Cataract	0.35	1.00	–	PB	–	–	7
9/63/F	Cataract	0.01	1.00	–	PB/mS	–	–	6
10/75/F	Cataract	0.2	1.00	–	–	–	+	6
11/66/F	Cataract	0.03	0.7	+□	–	–	+*	20
12/81/M	Cataract	0.01	0.7	–	PSX	–	–	9
13/77/M	Cataract	0.3	0.6	+	–	+	–	7

HM, hand motion; ME, macular edema; minus sign, no; plus sign; yes; □ indicates a cystoid edema; PB, leakage from pupillary border; mS, minimal leakage from stroma; PSX, pseudoexfoliation iridopathy; * indicates macular pucker.

Results

Results and complications of transcleral IOL fixation in each patient are summarized in Table 1. Mean best corrected visual acuity at the end of follow-up was 0.29 (SD 0.34; range 0.01–1.0) preoperatively and 0.71 (SD 0.21; range 0.4–1.0) postoperatively. In 11 eyes visual acuity improved by two or more lines, while remained unchanged to 1.0 in the two aphakic patients. In the patient with the retained lens nucleus and IOL dislocated into the vitreous preoperative visual acuity was 0.01 and 0.9 postoperatively. At the end of follow-up twelve patients had a best corrected visual acuity of 0.5 or better.

In 7 eyes both haptics were sutured to the ciliary sulcus and in 6 one haptic only was fixated. The lens was centered in all the eyes, tilting of the IOL was not evident in any case and none of the patients complained of diplopia. In none of the eyes were vitreous strands in the anterior chamber or in the wound present. No serious complications were recorded during trans-sulcus scleral fixation. Transitory vitreous hemorrhage occurred in 2 patients without sequelae. Hemorrhages disappeared within two weeks. There was no evidence of persistent IOP elevation.

Fundus biomicroscopy showed the presence of a cellophane maculopathy in three eyes and macular pucker in one eye. In 7 eyes the iris angiogram did not show appreciable areas of dye leakage. Dye leakage from the pupillary border was present in 3 eyes. Dye leakage from the pupillary border and minimal focal leakage from the stroma were evident in 2 eyes. One eye showed the typical iris vascular pattern of pseudoexfoliation syndrome with focal microvascular anomalies. Retinal angiography disclosed five cases of fluorescein leakage in the macular area. In two of them, cystoid macular edema (CME) was evident. In six eyes operating microscope light-induced phototoxic retinal lesions occurred. All the burns were extrafoveal and none of the patients complained of symptoms. The lesions were well identifiable with fluorescein angiogram and scarcely visible with fundus biomicroscopy in most cases.

Discussion

Malbran et al. were the first to describe transsulcus scleral fixation of posterior chamber IOLs in aphakic eyes that previously underwent an intracapsular cataract extraction [1]. In a recent survey, corneal surgeons were asked about their technique of suture fixation of posterior chamber intraocular lenses in the absence of posterior capsule support. Scleral fixation was marginally favored over iris fixation by these surgeons [2]. So far a number

of techniques have been proposed and none of them has clearly emerged as the optimal method for IOL fixation without capsular support.

Bleckmann et al. recently reported the functional results of posterior chamber lens implantation with scleral fixation in a group of 18 aphakic patients unable to tolerate contact lenses after intracapsular cataract extraction or with capsular rupture [3]. Mean visual acuity before lens implantation was 0.6 ($\pm$ 0.2) and 0.7 ($\pm$ 0.009) postoperatively. The visual quotient was nearly constant at 0.87 preoperatively and 0.9 postoperatively, which indicates that visual acuity was virtually unchanged after lens implantation. In seven aphakic eyes where transsulcus scleral fixation of a IOL was performed, Hahn et al. reported a best corrected postoperative visual acuity of 0.5 or better in 57.1% of patients. The postoperative corrected visual acuity was either the same or within one Snellen line of best corrected preoperative vision in all cases during the follow-up of 9 to 13 months. There were no complications associated with the procedure [4]. Similarly in the two aphakic patients of our series visual acuity was stable. Grehn et al., using a transscleral fixation technique in 10 patients with large rupture of the posterior capsule reported a postoperative mean visual acuity of 0.25. Mean visual acuity was 0.1 preoperatively [5]. Stark at al. used a transscleral IOL fixation technique in 16 contact lens-intolerant patients with aphakia and in 8 eyes at the time of IOL removal. In 83.3% of cases postoperative visual acuity was 0.5 or better [6]. In our study 92.3% of our patients achieved a visual acuity of 0.5 or better. The mean best corrected visual acuity was 0.71 postoperatively. Although differences in ocular conditions should be considered – i.e. aphakia, pseudophakia, intraoperative capsular rupture during cataract extraction – our results for visual acuity do not differ from those of other studies.

In our series one or two haptics of the IOL were sutured to the sulcus. When only one haptic was fixated the suture was carefully tightened in order to avoid the decentration of the lens. We implanted IOLs with loops placed along the haptics to reduce the occurrence of suture slippage along the haptic or tilt of the lens. Some authors showed that the IOL may tilt or decenter if fixated at two points [7]. This could negatively affect vision and refraction. Lee et al. showed that the tilt or decentration caused by two-point fixation had little effect on postoperative vision and astigmatism [8]. Similarly Bleckmann et al. indicated that decentration of less of 2 mm. is not associated with diplopia or deviation from desired refraction and tilting in the sagittal plane does not seem to have a major effect on postoperative refraction [3].

We were concerned that the transscleral procedure might be associated with a high rate of hyphema and vitreous hemorrhage. Bleckmann et al. found that these were the principal complications of the procedure though all intraocular hemorrhages disappeared within ten days without sequelae

[3]. Bleeding has not been a problem in our cases. Therefore it would seem that intraoperative hemorrhage is not a serious complication of scleral fixation. We performed an extensive anterior vitrectomy with a proper amount of viscoelastic substance. The vitrectomy must be performed carefully without leaving vitreous strands or lens remnants which may cause retinal traction and inflammation. However, in four patients fundus biomicroscopy and fluorescein angiography disclosed the presence of cellophane maculopathy or macular pucker which were not noted before surgery. The risk of vitreomacular traction syndrome and epiretinal membranes is always present following anterior vitrectomy. The occurrence of these complications may be a cause of poor visual recovery after surgery.

In case of complicated cataract surgery with vitreous strands into the wound or in the anterior chamber, diffuse dye leakage from iris vessels is a common finding. The increase of vessels permeability may be representative of an iridocyclitis due to irritation from the IOL or the presence of vitreous strands. In this study transsclerally sutured IOLs with a meticulous anterior vitrectomy comprehensive of removal of the lens remnants do not seem to be associated to a significant increase of iris permeability.

Cystoid macular edema (CME) has been reported as the most common postoperative complication by several authors [4,9]. On the contrary in a study by Stark et al. on secondary posterior chamber IOL implantation, no eyes had clinically significant CME and no persistent angiographic CME developed [6]. In our study 5 of 13 eyes had an angiographic macular edema which was the major cause of lower visual recovery after implantation. The causes of CME following cataract surgery are mechanical (vitreous strands or iris in the wound, vitreomacular traction), iatrogenic (instillation of adrenaline and its derivatives), inflammatory (chronic iris irritation) and physical (ultraviolet radiation reaching the retina at the time of surgery). Blood-retinal barrier disturbances secondary to degenerative vitreous changes have also been suggested [10]. Considering that iris fluorescein angiogram findings did not show major abnormalities we excluded the presence of iridocyclitis as the cause of macular edema. We suppose that macular edema might have been related to mechanical factors due to vitreous changes following surgery. The operating microscope illumination might exert a role also, as the duration of surgery is considerable [11]. As this study did not account for different rates of follow-up at different time intervals in the assessment of macular edema, the rate of this complication might also decrease with the progression of follow-up.

McDonald and Irvine were the first to report on light-induced retinal injury from the operating microscope in cataract surgery [11]. A series of risk factors have been described. Prolonged operating time has probably a major

role [12]. The incidence of light-induced retinal injury from the operating microscope in cataract surgery varies from 0% to 7% to 28% depending on the studies [13–15]. A retinal lesion consistent with photic injury was found in 6 eyes in this study. Prolonged operating time together with the lack of physiological protective mechanisms of the eye probably determined excessive light levels to the retina and light-induced injuries occurred. The light of the operating microscope reached the posterior pole through the dilated pupil without the filtering effect of the crystalline lens, especially during the period spent to create the scleral flaps, to suture the haptics of the IOL, for a meticulous vitrectomy and to implant the IOL.

The lesions were asymptomatic and scarcely visible ophthalmoscopically. Although this is the first report on intraoperative light-induced retinal injuries during transscleral IOL fixation we suppose that their occurrence is a common finding during this procedure. Given these results, it might be advisable to shield the pupil with an opaque barrier during some phases of surgery.

Our technique is a modification of that described by Malbran et al. in 1986 and allows a posterior chamber IOL implantation in the absence of the posterior capsule support [1]. Although the procedure guarantees a best corrected visual acuity of 0.5 or better in the majority of patients retinal complications were not uncommon. The occurrence of macular edema and cellophane maculopathy might determine a low visual recovery after surgery. Light-induced retinal injury seems to be a frequent permanent intraoperative complication.

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Macular edema induced by phacoemulsification

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Abstract. *Purpose:* To characterise the association between lens phacoemulsification and the development of macular edema. *Methods*: We studied 15 patients who underwent lens phacoemulsification in our clinic between January and April 1998 performed by the same surgeon. Ultrasound power and cumulative time was noted. Follow-up was performed at 1 day, 1 week, 1, 3 and 6 months after operation. On each visit corneal thickness, best corrected visual acuity, biomicroscopy and fluorescein angiography were performed. Patients with systemic diseases and/or retinal diseases were not included. *Results*: Visual acuity was inversely related to the amount of energy delivered during phacoemulsification. In patients who had received more than 1 Joule of energy, fluorescein angiography revealed a higher incidence of blood retinal barrier breakdown. Corneal thickness was not correlated with the ultrasound energy used. *Conclusions*: Excessive use of power during phacoemulsification may hamper the postoperative evolution of cataract surgery.

Key words: cataract, cornea, fluorescein angiography, macular edema, phacoemulsification, visual acuity

Introduction

The complication of macular edema, which may develop after cataract extraction, has been known for many years [1, 2]. Since the introduction of phacoemulsification, which represents a less traumatic way to extract the lens, the incidence of macular edema has dropped [3]. However, excessive use of power of phaco may lead to a mitigated visual recovery. The present study aims to investigate the effect of excessive power of phaco on the postoperative retinal function.

Patients and methods

We studied 15 eyes of 15 patients with a mean age of 64.6±5.8 years (6 males, 9 females). All patients had straight forward age-related cataract. Inclusion criteria were: Age between 55 and 75 years, lens hardness of D2 and D3, no anterior or posterior segment affections, and no systemic diseases such as renal failure, systemic hypertension or diabetes. Patients who developed

intraoperative capsular rupture, endophthalmitis, massive alteration of the intraocular pressure, or patients where the implant had to be placed in the sulcus or into the anterior chamber were not included in this study. Phacoemulsification of the lens was performed by the same surgeon. All patients' pupils were dilated with tropycamide 1% and operated with topical anesthesia using propacaine 1% eye drops. All phacoemulsifications were performed using the ALCON Legacy 2000 system between January and April 1998. All patients received a silicon intraocular lens (S140) in the posterior chamber. One day after the operation the patients were discharged with topical therapy of N-Methilmicine, F-metholone and tropycamide as well as with a systemic treatment of norfloxacine 500 mg per os BID. Ultrasound power, cumulative time of phaco and overall length of the operation was noted. Patients were then followed up after 1 day, 1 week, 1, 3 and 6 months in a double blind study by two medical retina specialists. On each visit corneal thickness by pachymetry, best corrected visual acuity, slitlamp biomicroscopy and fluorescein angiography were performed.

Results

The analysis of final visual acuity and of delivered energy of phaco (Joules) showed a clearly lower vision in patients in which higher energies have been used during the operation (correlation at 14 days: P=0.017; at 30 days: P=0.005; at 60 days: P=0.009). We further analysed two subgroups made of patients who had received less than 1 Joule of phaco energy, and patients who had received more than 1 Joule. The mean visual acuity in those two groups did not differ significantly. However, looking at the fluorescein angiograms, blood retinal barrier breakdown was much more commonly seen in the group in which more than 1 Joule of phaco energy had been delivered. Mean visual acuity was also significantly lower in patients whose operation had lasted longer ($P<0.05$). We only found, finally, a correlation between increased postoperative corneal thickness and the amount of energy of phaco used just after 14 days of follow-up; the final visit did not show this correlation anymore.

Discussion

The amount of phacoemulsification energy used during cataract extraction may be directly correlated to a poorer visual recovery after surgery. This may be due to increased blood retinal barrier breakdown in eyes with consecutive macular edema. Increased operation length may also lead to similar effects.

Using less than 1 Joule of power during phacoemulsification may lead to a good postoperative outcome.

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Cyst formation in optic disc pit maculopathy

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Abstract. *Purpose:* To evaluate the presence and the evolution of cyst formation in optic disc pit maculopathy. *Methods:* In this prospective study, 18 cases with optic disc pit maculopathy were studied. Five of them showed cyst formation in the fovea at the initial examination. The fundus findings were documented with slit-lamp biomicroscopy, indirect ophthalmoscopy, and stereoscopic photography of the posterior pole. All 5 patients were treated with a macular scleral buckle procedure. *Results:* The presence of cysts in the elevated macula depends on the grade of the disease. Cyst formation can develop not only in the later stage of the disease but also quite early. In all 5 patients cyst formation gradually decreased and finally disappeared after the surgical procedure. *Conclusions:* Cyst formation is an entity which accompanies the macular detachment associated with optic disc pit. The development of the cysts has been noticed after the establishment of the schisis-like separation and before or in conjunction with the formation of a lamellar macular hole which usually accompanies the optic disc pit maculopathy.

Introduction

A congenital pit of the optic nerve is a rare abnormality. Approximately 25–75% of patients with optic disc pit have an associated macular detachment, and long standing detachment in the macula leads to the formation of cystic degeneration and lamellar macular holes. [1–5]. Full thickness macular holes and rhegmatogenous retinal detachment can occur but very rarely. [6]

Optical coherence tomography (OCT) combined with stereoscopic fundus examination in optic disc pit maculopathy have recently shown that the macular elevation in the early stages of the disease seems to be a schisis like splitting of the neurosensory retina which emanates from the optic disc pit. At a later stage a lamellar macular hole and an outer layer retinal detachment develop. In a number of cases with optic disc pit maculopathy the presence of cyst formation alone or in association with lamellar macular holes can be found.

The purpose of this prospective study is to present 5 cases of optic disc pit maculopathy with cyst formation and to describe their evolution before and after treatment with the macular buckling procedure.

Patients and methods

A consecutive series of 18 patients , 10 males and 8 females with unilateral optic disc pit maculopathy were examined between May 1991 and January 1998. Five of them were found to have cysts in the area of the elevated macula. The fundus of each of the 18 patients was examined before and after treatment with color stereoscopic photographs of the posterior pole, slit-lamp biomicroscopy and indirect ophthalmoscopy. Corrected Snellen visual acuities were also determined.

Results

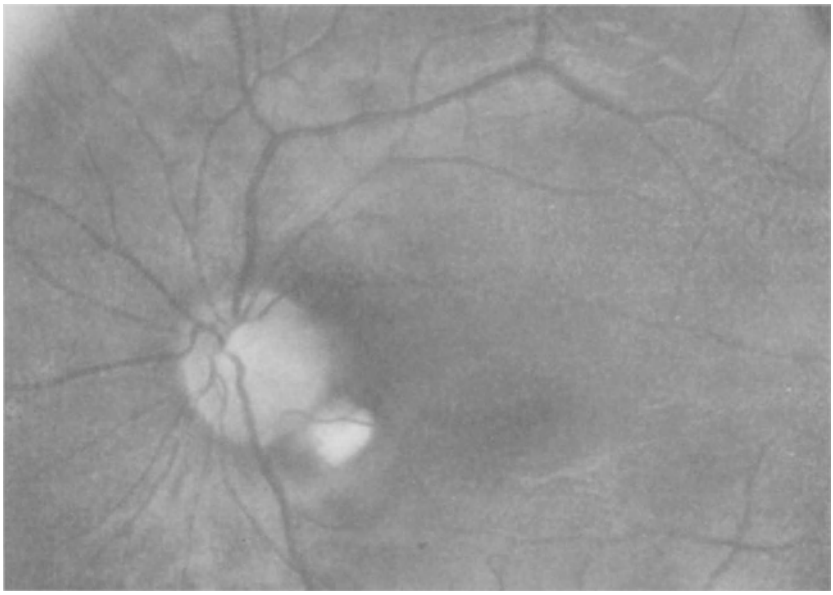
Demographics

Demographics of our patients are presented in Table 1. Three of them were women and 2 men. The patient's age ranged from 14 to 32 years at the time of the initial examination. Two patients were younger than 20 years when the visual symptoms started. All the optic disc pits were temporal. The visual acuity at initial examination varied from 20/64 to hand motion.

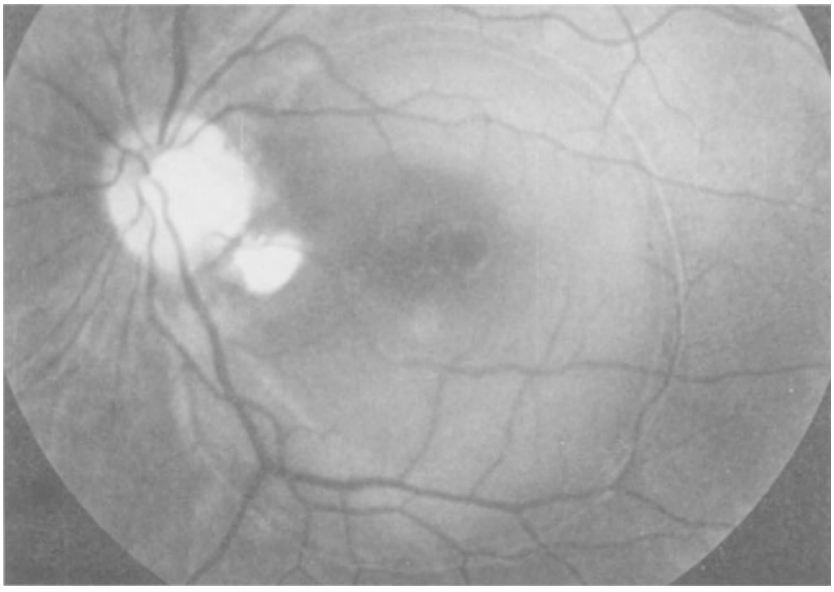
Findings of fundus examination

Results of the fundus examination and the stereo photographs are summarized in Table 1. The first two patients showed a transparent schisis-like separation of the internal layers of the retina (ILS) in the area of the macula which was accompanied by cyst formation in the foveola. One of these two patients did not accept the proposed surgical treatment at the initial examination. He returned for treatment 18 months later. At that time new cyst formations were observed which were located nasally to the macula while the preexisting cyst in the foveola had ended in a lamellar macular hole (Figures 1a and 1b). In the third case a schisis-like separation, confluent cysts and an outer layer detachment (OLD) were found. In the last two cases (Nos. 4 and 5) the schisis-like separation was accompanied by a lamellar macular hole, adjacent to a cyst formation and an outer layer detachment.

In all 5 cases the stereoscopic fundus photographs showed that the cyst formations were located in the outer layer of the retina. All 5 patients were



(a)



(b)

Figure 1. (a) (Case 1). Optic disc pit maculopathy. Note the schisis-like splitting of the macula and the cyst in the foveola. (Case 1). Same patient as in Figure 1b, eighteen months later. The preexisting cyst of the macula has ended into a lamellar macular hole. Moreover, two new cystic formations were found adjacent to the macula.

Table 1.

Patient's No. age at onset gender	Type of elevation	Macular appearance at first examination	Visual acuity in the first examination	Visual acuity after treatment
1. 17 M	Retinoschisis like separation	Cyst formation (first examination)		
		Lamellar macular holes adjacent cyst formation (18 months later)	20/64	20/40
2. 29 F	Retinoschisis like separation	Cystic formation	20/100	20/64
3. 14 F	Retinoschisis like separation, outer layer detachment	Confluent cysts	20/200	20/100
4. 32 M	Retinoschisis like separation, outer layer detachment	Lamellar macular hole adjacent holes	20/200	20/64
5. 23 M	Retinoschisis like separation, outer layer detachment	Lamellar macular hole adjacent cysts	H.M.*	20/200

*H.M. = Hand motion.

treated with the standard scleral macular buckling procedure [7]. No additional treatment of any kind (such as laser, diathery or cryotherapy) was used. The procedure consisted of fixing a silastic sponge 6.0 × 5.5 mm at the posterior pole of the globe corresponding to the macula along the vertical axis of the 12 to 6 o'clock meridian. The fixation of the upper end of the sponge corresponded to the posterior edge of the insertion of the superior oblique muscle. The lower end of the sponge was stretched and fixed at the temporal belly of the inferior rectus muscle. (Figure 2). Postoperative anatomic success was determined as the flattening of the macula and the surrounding area with no fluid present in the retina or external to the neurosensory retina. In all 5 cases anatomic success was attained. The flattening of the macula occurred

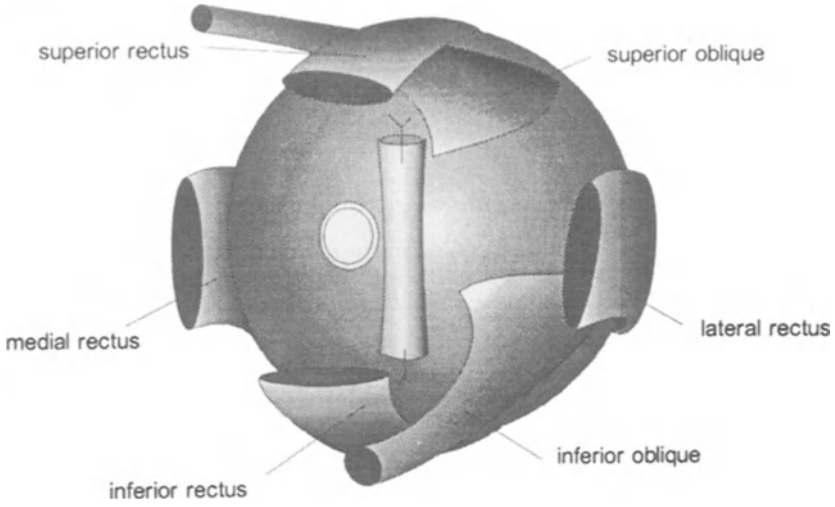


Figure 2. Illustration of the sponge fixation at the posterior part of the eyeball. The sponge seems to act as a barrier which prevents fluid flow from the pit to the macula.

gradually. More specifically the outer layer detachment disappeared in the first postoperative week. The flattening of the schisis-like splitting proceeded gradually and the fluid absorption was completed 6 months after the operation. The cyst formation and the lamellar macular hole gradually became less recognizable and finally disappeared leaving, however, a slightly wrinkled macula remained.

Discussion

Cystic degeneration has been described in long standing optic disc pit maculopathy. Recently, Rutledge et al. [8] have studied 4 cases with OCT and found the presence of cystic degeneration overlying the macular neurosensory detachment. However, so far no specific reference has been made related to the form and the evolution of cystic formations which accompany the optic disc pit macular elevation.

The fundus stereo photographs of our 5 cases have shown the presence of cyst formation located in the outer layers of the retina. Even though we do not know exactly the evolution of the optic disc pit maculopathy we can postulate that there are some grades of the disease. In the first grade, which could also be called early stage, we have the appearance of schisis-like separation in the inner layers of the retina emanating from the optic disc pit. In a more advanced stage (third grade) the schisis-like separation is associated with a

lamellar macular hole and an outer layer detachment. Probably the cyst formation appears for the first time in an intermediate stage (grade 2) and before the formation of the lamellar macular hole. Presumably, the pre-existing cyst formation in the outer layer of the retina ends as a lamellar macular hole which can be associated with the development of an outer layer detachment. In some instances, the coexistence of a lamellar macular hole with cyst formation located in the adjacent area of the retina was also found (cases Nos. 4 and 5). The evolution of the cysts is more evident in case 1 where the second examination showed that the pre-existing cyst formations had ended into a lamellar macular hole. Moreover, two new cysts were observed for the first time in the adjacent retina (the interval between the 1st and 2nd examination was 18 months). These findings support the view that the cyst formation is not only observed in the advanced stages of the disease but that it can also be found earlier.

The visual acuity of the 5 studied cases was directly related to the changes and the findings of the elevated macula. More specifically, in the two first cases where the cysts coexisted only with a schisis-like separation, the visual acuity was 20/64 and 20/100 respectively. In more advanced stages with the presence of cysts, lamellar macular hole and an outer layer detachment, visual acuity was 20/200 in cases 3 and 4 , and hand motion in case 5. After the successful macular buckling procedure the visual acuity improved (Table 1). Moreover, the cysts gradually faded and finally disappeared after the absorption of the submacular fluid. The analysis of the findings of our 5 cases has shown that the presence of cysts in optic disc pit maculopathy is not an unusual phenomenon and that their presence seems to be related to the grade of the disease.

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Optical coherence tomography (OCT) in macular edema

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Introduction

Optical coherence tomography (OCT) is a new retinal imaging technique that produces cross-sectional images of the retina [1–5]. Imaging with OCT is analogous to ultrasound B-scan. The use of optical rather than acoustic waves, however, provides much higher resolution of the retina. Theoretically this resolution is in the order of 10 μm, but in a clinical setting it is more in the region of 15–20 μm. In this article we used OCT to evaluate macular edema secondary to diabetic retinopathy, retinal vein occlusion, uveitis and epiretinal membranes. We also measured central retinal thickness before and after laser photocoagulation, in order to evaluate and follow the efficacy of the therapy.

Methods

Patients with diabetic retinopathy, retinal vein occlusion, uveitis and epiretinal membranes underwent OCT examination. A series of vertical OCT scans, obtained through the macula, provided three dimensional information on retinal structure. The images were illustrated in a false color scheme, where brighter colors (white and red) represented region of high optical reflectivity and darker colors (blue and black) corresponded to regions of lower relative reflectivity.

Measurements of central macular thickness were obtained directly from OCT by using computer software controlled cursors that were manually placed on the superficial and deep retina boundaries.

Results

The OCT image of the retinal layers, although obtained through reflectance

measurements, turns out to be fairly well overlapping with the histological appearance of the same layers [4].

In all the patients with macular edema , the retinal thickness was increased and was visible as an area of low reflectivity in the outer retinal layers. We could differentiate cystoid and diffuse edema.

In the cystoid edema, low reflective spaces, divided by thin hyperreflective membranes, corresponded to cystic spaces in the outer plexiform and inner nuclear layers. A large central cyst was occasionally noted to extend to the inner limiting membrane. The reduced optical reflectivity was caused by the intraretinal fluid accumulation. In diffuse edema, a continous area of low reflectivity was present in the retina. It is possible moreover to consider two types of edema on the basis of different pathogenesis: non-tractional or tractional edema. In diabetic patients and in patients with retinal vein occlusion we observed a reduced macular thickness after laser photocoagulation. In patients with uveitis it was possible to follow the efficacy of medical therapy employed to reduce macular edema. We also considered two types of epiretinal membranes: adherent to the retina, or separated from the retina.

Epiretinal membranes were identified from the OCT when they were separated from the inner margin of the retina. The OCT showed a thin reflective band anterior to the retina. When the epiretinal membranes were tightly adherent to the retinal surface, they were identifiable by an increased reflective image of the retina. OCT was also able to provide a structural assessment of the macula in the preoperative and postoperative evaluation of epiretinal membranes [3]. OCT data appeared to be a good indicator for the successful removal of the epiretinal membranes and for decreasing retinal thickness after surgical intervention.

Conclusion

We demonstrated, with our article, the utility of OCT in identifying or confirming both edematous changes in macular thickness and tractional macular edema. OCT has also proved to be an effective tool for the evaluation and the follow up of macular fluid accumulation in several ocular pathologies.

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Novel imaging techniques for diabetic macular edema

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Abstract. Retinal edema should be defined as any increase of water of the retinal tissue resulting in an increase in its volume. It may be of cytotoxic or vasogenic origin. Development of vasogenic macular edema is dependent on a series of factors such as blood pressure, blood-retinal barrier permeability, retinal cell damage, retinal tissue osmotic pressure and retinal tissue compliance. Objective measurements of retinal thickness are now possible using the Retinal Thickness Analyser. Localised measurements of blood-retinal barrier permeability may also be obtained using the Retinal Leakage Analyser, a modified confocal scanning laser fluorometer, while obtaining simultaneously angiographic images of the choroid and retina. These new imaging techniques show that cytotoxic and vasogenic retinal edema may occur independently in the early stages of diabetic retinopathy. These findings offer new perpectives for designing novel therapeutic strategies.

Key words: diabetes, edema, imaging, retinal leakage analyser, retinal thickness analyser, retinopathy

Introduction

Diabetes is the leading cause of new cases of legal blindness among working age Americans. Insulin dependent diabetes mellitus (IDDM) or Type 1 carries a higher risk of ocular complications, but because there are many more patients with non-insulin dependent diabetes mellitus (Type 2), the latter group comprises a substantial proportion of patients with blinding sequelae. It has been estimated in the United States that there are almost 75,000 new cases of diabetic macular edema each year. These numbers are clearly on the rise, and it is expected that by the year 2010, 10% of the American population will suffer from diabetes, especially Type 2 [1].

Basic concepts of retinal edema

First, it is very important to define retinal edema. Retinal edema should clearly

be defined as any increase of water of the retinal tissue resulting in an increase in its volume, i.e., thickness.

This increase in water content of the retinal tissue may be initially intracellular or extracellular. In the first case, also called cytotoxic edema, there is an alteration of the cellular ionic exchanges with an excess of Na^+ inside the cell. In the second case, also called vasogenic edema, there is a predominantly extracellular accumulation of fluid directly associated with an alteration of the Blood-Retinal Barrier (BRB). In this latter situation Starling law applies and any loss of equilibrium between hydrostatic, oncotic and osmotic pressure gradients across the BRB contribute to further water movements and edema formation.

In cytotoxic edema, there is initially not a true edema, only a redistribution of water from its normal extracellular location to the intracellular space, causing cell damage, more edema and later release of vasoactive substances which may induce vasogenic edema through alteration of the BRB.

The initial alteration in intracellular, or cytotoxic, edema may be a lack of ATP^+ with depolarization of the cell membranes, alteration of the cell ionic pumps with an increase of extracellular K^+ with glutamate release and an increase of intracellular Ca^+ [2]. It may also result from an excitatory release of glutamate or lactic acidosis, activating Na^+/ H^+ transport and accumulation of intracellular Na^+.

Vasogenic edema results from a breakdown of the BRB with extracellular deposition of macromolecules. The primary defect is in the BRB and the accumulation of fluid is extracellular.

In this situation, the 'force' driving water across the capillary wall is the result of a hydrostatic pressure difference ΔP and an effective osmotic pressure difference $\Delta\pi\sigma$ [3]. The equation regulating movements across the BRB is, therefore:

$$(driving\ force) = Lp\ [(P_{plasma} - P_{tissue}) - \sigma(\pi_{plasma} - \pi_{tissue})]$$

where Lp is the hydraulic conductivity or membrane permeability of the BRB and σ, an osmotic reflection coefficient, P_{plasma}, the blood pressure, P_{tissue}, the retinal tissue pressure, π_{plasma}, blood osmotic pressure and π_{tissue}, the tissue osmotic pressure.

The loss of equilibrium between these pressure gradients is of importance only after alteration of the Blood-Retinal Barrier (BRB), contributing then to water movements.

An increase in ΔP, contributing to retinal edema, may be due to an increase in P_{plasma} or a decrease in P_{tissue} or both. An increase in P_{plasma} due to increased systemic blood pressure does contribute to retinal edema formation only after loss of autoregulation of retinal blood flow and alteration of the structural

characteristics of the BRB. A decrease in P_{tissue} is an important component that has not been given sufficient attention. Any loss in the cohesiveness of the retinal tissue due to pathologies such as cyst formation, vitreous traction, or pulling at the inner limiting membrane will lead to a decrease in P_{tissue}. A decrease in P_{tissue}, or increased retinal tissue compliance may lead to fluid accumulation, edema formation, and an increase in retinal thickness.

A decrease in $\Delta\pi$, contributing to retinal edema, may occur due to increased protein accumulation in the retina after breakdown of the BRB. Exsudate formation and extravasation of proteins will draw more water into the retina. This is the main factor provoking a decrease in $\Delta\pi$, as a reduction in plasma osmolarity high enough to contribute to edema formation is an extremely rare event.

After a breakdown of the BRB the progression of retinal edema depends directly on the ΔP and $\Delta\pi$ gradients. In these situations, tissue compliance becomes more important, influencing directly the rate of edema progression.

In summary: retinal edema may be, initially, exclusively intracellular or extracellular. In the first case, it occurs without breakdown of the BRB. In the second case, a breakdown of the BRB must be present.

Clinical evaluation of retinal edema

The clinical evaluation of macular edema has been characterized by its difficulty. Direct and indirect ophthalmoscopy may show only an alteration of the foveal reflexes. Stereoscopic fundus photography and slit-lamp microscopy play an important role demonstrating changes in retinal volume in the macular area but they are dependent on the observer experience and the results do not offer a reproducible measurement of the volume change. The Early Treatment Diabetic Retinopathy Study, defined that the following characteristics indicate "clinically significant macular edema":

(1) Thickening of the retina (as seen either by slit lamp biomicroscopy or by stereo fundus photography) at or within 500 microns of the center of the macula;

(2) Hard exsudates at or within 500 microns of the center of the macula, associated with the thickening of the adjacent retina (but not residual hard exsudates remaining after disappearance of retinal thickening); and

(3) A zone, or zones, of retinal thickening one disc area or larger size, any part of which is within one disc diameter of the center of the macula.

This definition was proposed to take into special consideration the involvement of the center of the macula and its relationship to visual loss.

Imaging of macular edema

We have seen that in order to develop retinal edema an increase in retinal volume must be present. This increase in volume is represented by an increase in retinal thickness because of the anatomical architecture of the retina. Recently, a new technique was become available that measures objectively overall retinal thickness, the Retinal Thickness Analyser (RTA) [4].

We have defined retinal edema as any increase of water of the retinal tissue resulting in an increase in its thickness. Any increase in retinal thickness is, therefore, a direct measurement of retinal edema. It is of particular interest that there are now two instruments capable of measuring non-invasively the thickness of the retina, the Retinal Thickness Analyser and Optical Coherence Tomography (OCT). Both methods depend on clear media but allow for very precise measurement of minor changes in retinal thickness. The Retinal Thickness Analyser measures a slit-lamp like image of the retina, using the internal limiting membrane and the retinal pigment epithelium as references. It is associated with reliable positioning in the retina and has very good reproducibility. It is of particular value in situations of retinal edema, without marked disorganization of the retina. Optical Coherence Tomography gives a color-coded image of the optical density of the various cellular components of the retina and is of special interest in the presence of advanced structural changes in the retina like cyst formation, and to demonstrate vitreal traction and surface abnormalitites of the retina.

BRB breakdown has been detected by fluorescein angiography and measured by vitreous fluorometry. It is now possible, using the Retinal Leakage Analyser (RLA), a new instrument developed by our group, to perform localised measurements of the permeability of the BRB with simultaneous imaging of the retina [5]. Thus, quantitative maps of retinal thickness and quantitative maps of retinal fluorescein leakage, indicative of BRB permeability can be obtained simultaneously, making sure that they are from the same location in the retina. All these examinations and measurements are performed in a clinical environment.

We have now, therefore, the means to acquire more data on retinal edema. By measuring retinal thickness we characterize the location of the edema and are capable of following its evolution. Next, it is important to determine whether it is associated with breakdown of the BRB, i.e., whether it is vasogenic. The absence of a breakdown of the BRB would indicate a situation of increased thickness due to intracellular or cytotoxic edema.

Furthermore, in a situation of vasogenic edema, information about ΔP and $\Delta\pi$ may be obtained using the OCT [6]. The presence of cysts and vitreal traction can be demonstrated very easily by this instrument, indicating loss of cohesiveness of the retinal tissue and demonstrating situations facilitating

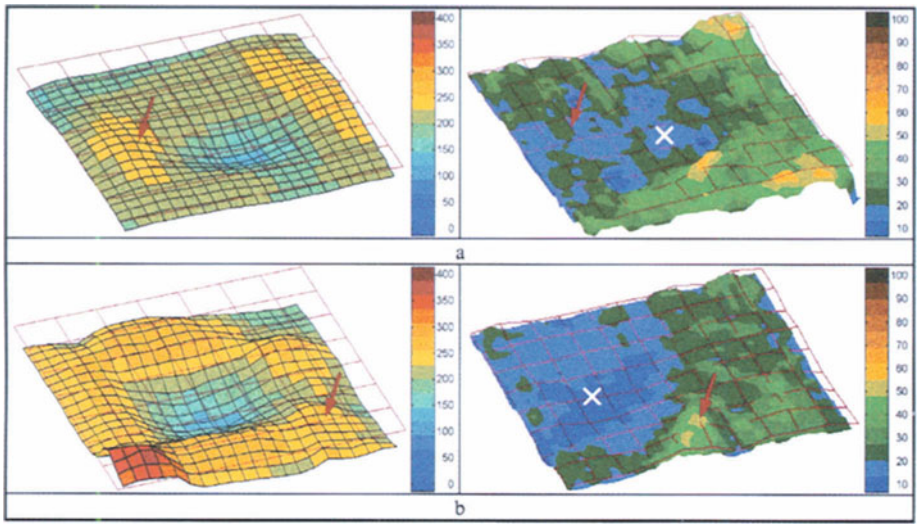

Figure 1. (a) Diabetic eye showing no visible signs of retinopathy on funduscopy. Left – RTA – map of retinal thickness (μm). Right – RLA – map of fluorescein leakage (10^{-7}cm/s) (normal values are in the range of blues and dark green; the white cross shows the center of the fovea). Note the presence of areas of thickening appearing independently from the leakage sites (arrows). (b). Diabetic eye with minimal retinopathy changes. Left – RTA – map of retinal thickness (μm). Right – RLA – map of fluorescein leakage (10^{-7}cm/s) (normal values are in the range of blues and dark green; the white cross shows the center of the fovea). Note the zones of increased thickness correlated to sites of increased fluorescein leakage (arrows).

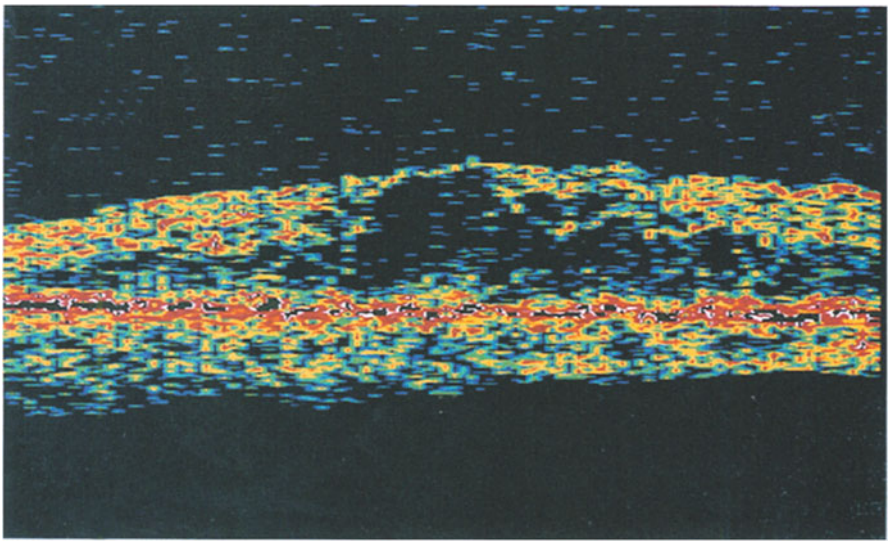

Figure 2. Image of Optical Coherence Tomography showing cyst formation in a situation of advanced diabetic macular edema.

fluid accumulation in the retina. Accumulation of proteins and exsudates in the retina may also become apparent as a localised increase of optical density of the retinal structures.

With these new imaging methods it is now possible to clinically follow retinal edema and to obtain information about its type (cytotoxic or vasogenic), as well as about other important factors involved in its progression.

Imaging of retinal edema in diabetes

The application of these new methods to the evaluation of diabetic macular edema has shown that both types of retinal edema, cytotoxic and vasogenic, occur in the diabetic retina before the development of clinical significant macular edema.

Preliminary results have shown that in diabetic eyes without vascular pathology visible on ophthalmoscopic examination it is possible to find localized areas of increased retinal thickness without associated breakdown of the BRB in the posterior pole (Figure 1a). However, in other locations it is possible to find a clear association between zones of increased thickness and sites of increased fluorescein leakage and breakdown of the BRB (Figure 1b).

We think that in the diabetic retina the two types of retinal edema occur together from the initial steps of the disease. Cytotoxic edema may well be the first. Recent results from our laboratory indicate that the retinal vessels increase glucose transport into the retina in the presence of hyperglycemia, thus creating an excessive accumulation of glucose in the inner retina [7]. Abnormally elevated glucose levels in the retina in diabetes lead to an increase in lactate and frutose production. The increase in the ratio lactate-pyruvate is similar to that induced by hypoxia. Williamson and co-workers [8] have called this a situation 'pseudo hypoxia' induced by the hyperglycemia. A natural outcome is the development of intracellular ionic changes and excessive glutamate release causing intracellular edema. Later on, progressive retinal cellular damage would result in the release of vasoactive substances such as nitric oxide and free radicals, inducing vascular damage and breakdown of the BRB with protein leakage and extracellular edema (vasogenic).

Studies directed to the earliest stages of retinal involvement of diabetes using simultaneously the RTA and the RLA are already offering new insights into our understanding of diabetic retinal disease and diabetic retinal edema. In more advanced situations of retinal pathology associated with marked retinal edema, OCT examination may show alterations in retinal structure and cyst formation (Figure 2).

A better targeted therapy of diabetic retinal edema will be derived from the application of these new methods of retinal imaging.

In diabetic macular edema, determining which type of retinal edema predominates (cytotoxic or vasogenic) may, in the future, influence the choice of neuroprotective or vasoprotective agents. Neuroprotective agents that are likely candidates include calcium-channel blockers, glutamate-receptor antagonists and antioxidants. Some of the vasoprotective agents that offer promising perspectives are nitric oxide synthethase inhibitors, Advanced Glycation Endproduct (AGE) formation inhibitors and Angiotensin Conversion Enzyme (ACE) inhibitors [9–11].

These drugs may be used in the near future to protect the retinal cells and the BRB from the damage caused by the increased and abnormal glucose metabolism occurring in the diabetic retina and thus delay the development of the retinopathy.

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Reproducibility of volumetric macular measurements in diabetic patients with the Heidelberg Retina Tomograph

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Abstract. *Aims*: To quantify diabetic macular edema by confocal scanning laser ophthalmoscopy and assess its usefulness by determining the reproducibility of topographic measurements at the macula. *Methods*: The volumes above reference plane bound by a 2 mm diameter circle centred on the fovea were measured by two observers. The reference plane was adjusted to the lowest point of the height variation of the contour line. The reproducibility of this technique was assessed in 20 eyes of 20 diabetic patients of which 8 eyes had macular edema. Three HRT scans of each eye were obtained. The measurements of volume above reference plane of each scan were repeated three times. *Results*: For all diabetic eyes, the intra scan coefficients of variability measured 14.71% to 21.21%, the inter scan coefficient of variability was 30.46%. The average standard deviations were 0.053 mm^3 for one examination per scan, 0.047 mm^3 for two examinations per scan and 0.044 mm^3 for three examinations per scan. Linear regression demonstrated an increase in standard deviation with greater volumetric measurements ($p < 0.001$). We found good correlation ($r = 0.959$, $p < 0.001$) and strong agreement between the two observer's findings for all 20 eyes. For the 8 eyes with macular edema, the coefficients of variability were similar to those calculated for all 20 eyes. The average SD for one examination per scan were 0.078 mm^3, 0.069 mm^3 for two examinations per scan and 0.062 mm^3 for three examinations per scan. We found good correlation ($r = 0.945$, $p < 0.001$) and strong agreement between the two observer's findings in eyes with edema. *Conclusion*: The reproducibility of this technique has been demonstrated in diabetic eyes. This may have useful clinical applications for the quantification of diabetic macular edema and monitoring of laser therapy.

Key words: diabetic maculopathy, Heidelberg Retina Tomograph (HRT), macular edema, reproducibility

Introduction

Macular edema is a major sight threatening complication of numerous systemic and ocular conditions. The evaluation of macular thickening by slitlamp biomicroscopy and stereo fundus photography are relatively insensitive to small changes in retinal thickness [1]. There is also evidence that the degree of

fluid accumulation is not reliably measured by angiographically demonstrated leakage [2, 3]. Retinal thickness analysis (RTA) images the macula by providing high speed cross sectional imaging of the retina [1, 2, 4]. Other methods for *in vivo* assessment of macular edema include digitised fundus fluorescein angiography (FFA) generated with a scanning laser ophthalmoscope (SLO) [5] and optical coherence tomography [6]. Furthermore, the reflectance intensity versus scan depth (termed 'Z' profile) using the Heidelberg Retina Tomograph (HRT) was described as an index of retinal thickening in 2 cases of diabetic macular edema [7]. Previous work documenting the features of the normal human 'Z' profile and its variations in different retinal locations were also described [8].

The reproducibility of the HRT in the evaluation of optic nerve topography, cup and rim volume as well as other parameters [9, 10], does not necessarily apply to the topographic measurements at the macula. We have previously described a new method for the detection and quantification of diabetic macular edema by volumetric analysis with the HRT using the software version 1.11 provided by Heidelberg [11] as well as the reproducibility of measured volumes in normal maculae and the variation observed across the age range [12]. The aim of this study is to assess the reproducibility and inter individual variability of this technique in 20 diabetic eyes.

Patients and methods

Technical details of the instrument have been described elsewhere [10]. The image acquisition and technique description have been described in our previous publication [11]. In short, all HRT scans were obtained after cycloplegia using cyclopentolate 1% and phenylephrine 2.5%. All images were centred on the fovea and a 2 mm dia. circle was drawn using the circle draw facility (Figures 1 and 2). The circle centre was the fovea. The scaling was adjusted to 25 mm in order to magnify any irregularities of the contour line before the reference plane was positioned to ensure the accurate positioning of the reference plane. The height of any point on the circle is given by the contour line in green (Figures 1 and 2). The reference plane shown in red (Figures 1 and 2) was adjusted to the lowest point of the contour line and the volume above reference plane was calculated by the computer software [11]. Thus the computer calculates the volume of a 2 mm dia. 'disc' of retina above the reference plane in a similar manner to the volume of nerve fibres in the optic nerve head.

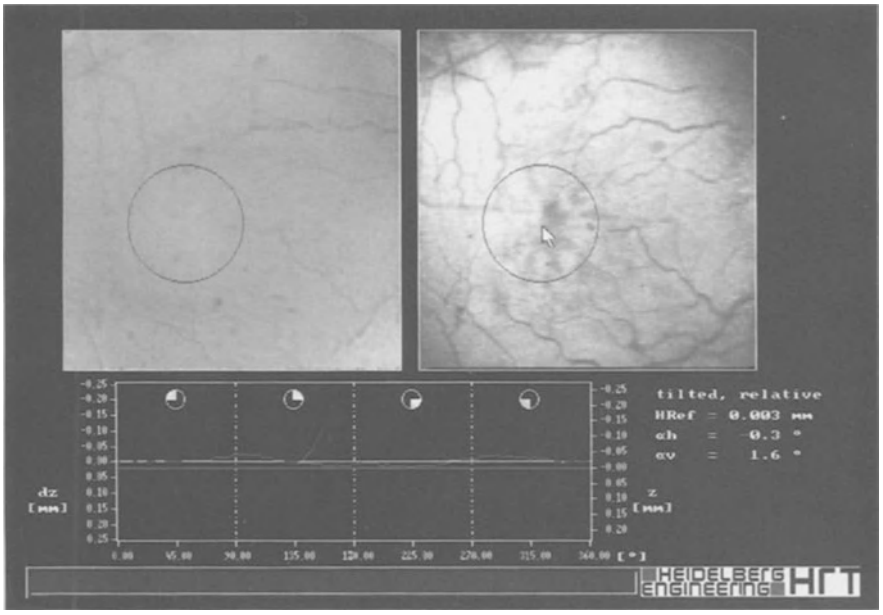

Figure 1. HRT scan of a diabetic macula (with no edema) centred at the fovea. The circle drawn using the circle draw facility is also centred at the fovea (arrow), the height variation of the contour line (in green) is almost flat indicating no significant topographic variation. The reference plane (in red) is adjusted to the lowest point of the contour line. The scaling is adjusted to 25 mm (left hand vertical axis).

Study eyes

20 eyes of 20 diabetic patients with retinopathy were included in the study. All subjects underwent a complete ophthalmic examination, including Snellen visual acuity, slit-lamp biomicroscopy, and dilated stereoscopic ophthalmoscopy with a yellow coated 78 dioptre (D) Volk lens by one of two experienced examiners (HJZ and SAV). Eyes with borderline or early macular thickening were also examined with a Goldmann posterior pole contact lens. There were 8 eyes with macular edema located within the 2 mm dia. circle centred at the fovea.

HRT scans were obtained by one experienced SLO operator (HJZ). All eyes were within 6.00 D of emmetropia (best sphere range −6.00 to + 4.00 D) with a maximum cylindrical correction of ± 1.50 D. Mean age was 59.15 years (range 30 to 76). The subjects' corrected visual acuity ranged from 20/40 to 20/15 (mean 20/30 obtained after anti logging the mean logarithm of the minimal angle of resolution).

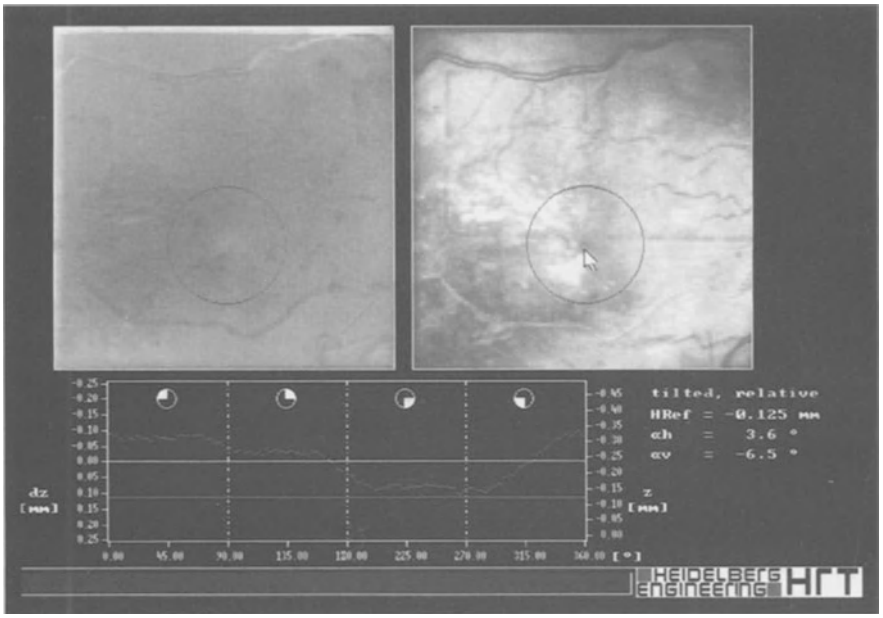

Figure 2. HRT scan of the right macula of a 57 year old diabetic lady with clinically significant macular edema. The height variation of the contour line (in green) demonstrates the presence of retinal thickening temporal, superior and inferior to the fovea (arrow). The scaling is adjusted to 25 mm (left hand vertical axis).

Informed consent was obtained for every subject which adhered to the tenets of the Declaration of Helsinki. The study protocol had ethical committee approval by the review board of the Queen's Medical Centre of the University Hospital of Nottingham.

Reproducibility

Theee scans of each eye were obtained by the method described. The subjects were asked to sit back between each scan and the head position was readjusted in order to simulate a separate examination. Each of two independent observers then measured the volume above reference plane within a 2 mm dia. circle by the method described above. To examine the repeatability of measurements, each circle was drawn three times on each of three days for every scan giving a total of 3 examinations per scan for each observer. At each stage the passive observer noted the measurements obtained so that the results were masked from the active observer. In each case the passive observer was also 'masked' in that she was not able to see the circle centre chosen by the active observer. The passive observer then became active and repeated

the measurements in a similar manner. The circles were erased after every examination so that the centre (the fovea) and the reference plane had to be redefined every time.

Statistical analysis

Intra observer variability was assessed by regression equations and by calculation of coefficients of variability (CV). The latter were calculated as the square root of the mean value of the variance of the measurements divided by the mean measured volume above reference plane.

Agreement between measurements were measured by techniques described by Bland and Altman [13]. As the differences were related to the mean over the range of measurements, a logarithmic transformation of the data was performed [13]. Bias between scans was assessed using difference vs. mean plots of the mean log transformed volume above reference plane of three examinations of each scan [13].

Linear regression analysis was performed to determine the relationship between the standard deviation (SD) of nine examinations of each eye and volumetric measurements. As other authors have used the average SD as a measure of reproducibility, we have calculated the average SD of one examination per scan and performed similar calculations for the mean of two and three examinations per scan.

The reproducibility of measuring volume above reference plane by this technique is assessed for all 20 diabetic eyes. However, as the reproducibility for the subgroup of 8 eyes with edema may be different due to the potential difficulty in accurately localising the fovea, we have repeated the above calculations for that subgroup separately. Findings with an error probability value of less than 0.05 were considered statistically significant.

Results

Intra observer variability for all eyes (Observer 1)

The mean volume above reference plane for all 20 eyes was 0.206 ± 0.12 mm^3. There was good correlation between the mean of three examinations of each scan ($r > 0.853$, $p < 0.001$). The volume above reference plane data were log-transformed and agreement between scans was examined by plotting the difference against the mean of the mean log values of each scan. We found good agreement as the mean differences did not significantly differ from zero, neither scan tended to read higher or lower than the other as volumes increased, and the slope of the regression lines were not significant (Figure 3, Table 1).

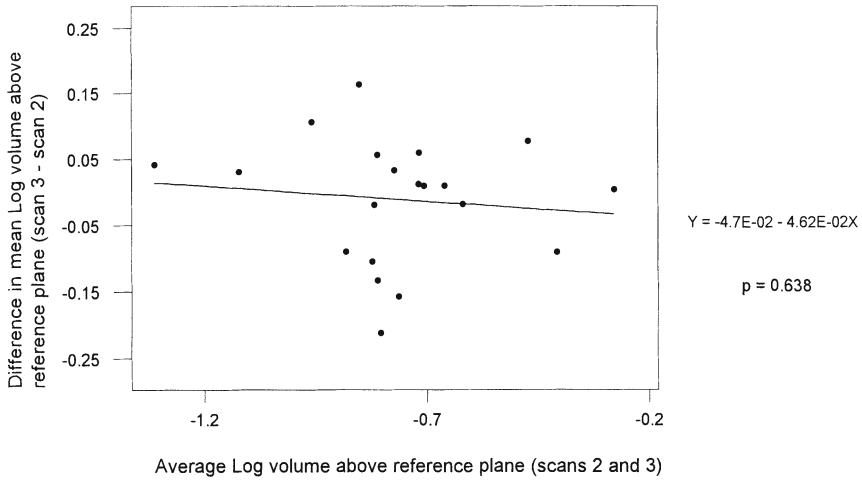

Figure 3. Agreement between scans 2 and 3. The means of the log transformed data for the volumes above reference plane of all 20 diabetic eyes were calculated and the differences against the means plotted for scans 2 and 3. The mean difference is −0.011, the slope of the regression line is not significant ($p = 0.638$) indicating good agreement between the two scans.

Table 1. Intra observer variability: The volume above reference plane data were log transformed and the means of the log data calculated. Agreement was assessed by regressing the differences against the means. The mean differences approached zero and the slope of the regression lines were not significant

	All 20 diabetic eyes			8 diabetic eyes with edema		
	Scan 1 vs. scan 2	Scan 1 vs. scan 3	Scan 2 vs. scan 3	Scan 1 vs. scan 2	Scan 1 vs. scan 3	Scan 2 vs. scan 3
Mean difference of log transformed data	−0.030	−0.042	−0.011	−0.143	−0.143	−0.037
Slope of the regression line	−0.225	−0.282	−0.046	−0.088	−0.120	−0.026
P value	0.115	0.101	0.638	0.719	0.700	0.886

The *intra scan* CV were 21.21% for scan 1, 14.71% for scan 2 and 17.84% for scan 3. However the *inter scan* CV was 30.46%.

The average SD of the first examination of each scan over the three scans was calculated as a further measure of reproducibility. The same calculations were repeated for the mean of two and three examinations per scan. The SD were 0.053 mm^3 for one examination per scan, 0.047 mm^3 for two examinations per scan and 0.044 mm^3 for three examinations per scan. These results however did not reach statistical significance when the SD of one examination per scan over three scans were compared to the SD of three examinations per scan with a Mann-Whitney U test ($p = 0.617$).

The SD of all 9 examinations of the three scans (three examinations per scan) were compared to the mean measured volume above reference plane. The slope of the regression line was significant ($Y = -2.9E\text{-}03 + 0.248\ X$, $p < 0.001$) demonstrating an increase in SD as the absolute volumetric measurements increased. However, linear regression analysis showed no significant trend in the SD throughout the age range ($Y = 0.107 - 9.79E\text{-}04\ X$, $p = 0.279$).

Inter observer variability for all 20 eyes

There was no significant difference between the mean of nine measurements for all 20 eyes made by the two observers ($p = 0.935$). We found a significant correlation ($r = 0.959$, $p < 0.001$) between the two observer's findings. Agreement was examined by plotting the difference against the mean of the means of the log transformed data for each of the three scans. We found good agreement as the slopes of the regression lines were not significant (Figure 4, Table 2) for all three scans.

Intra observer variability for the 8 eyes with edema within the 2 mm diameter circle (Observer 1)

The mean volume above reference plane for the 8 eyes with edema was 0.26 $\pm$ 0.144 mm^3. There was a good correlation between the mean of three examinations of each scan ($r > 0.771$, $p < 0.05$). Agreement was calculated after the volumetric data were log transformed by the same method described above. The mean differences approached zero and the slopes of the regression lines did not differ significantly from zero (Table 1).

The *intra scan* CV were 23.57% for scan 1, 16.40% for scan 2 and 22.36% for scan 3. The *inter scan* CV increased to 31.76%.

The average SD for one examination per scan were 0.078 mm^3, 0.069 mm^3 for two examinations per scan and 0.062 $mm^3$for three examinations per scan. These results did not reach statistical significance when the SD of

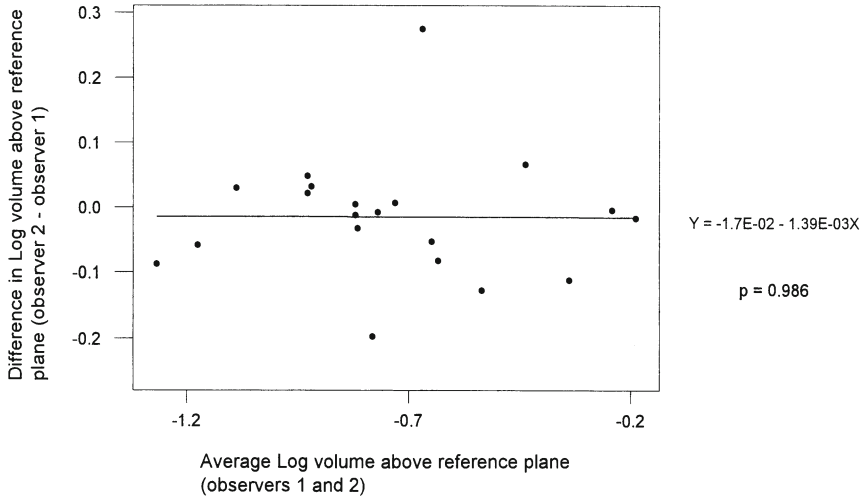

Figure 4. Agreement between observers 1 and 2 on scan 1 (Inter observer variability for all 20 diabetic eyes). The means of the log transformed data for the volumes above reference plane were calculated and the differences against the means plotted for scan 1. The mean difference of the log volume above reference plane is −0.011, the slope of the regression line is not significant ($p = 0.986$) indicating good agreement between the two observers.

Table 2. Inter observer variability: The means of the log transformed data for the volumes above reference plane were calculated and the differences against the means plotted for all three scans. The mean differences between the two observers approached zero and the slopes of the regression lines were not significant indicating good agreement between the two observers

	All 20 diabetic eyes			8 diabetic eyes with edema		
	Scan 1	Scan 2	Scan 3	Scan 1	Scan 2	Scan 3
Mean difference log transformed data	−0.011	−0.011	−0.010	−0.054	−0.026	0.009
Slope of the regression line	−0.001	−0.003	0.120	0.015	−0.110	−0.065
P value	0.986	0.946	0.147	0.916	0.109	0.679

one examination of one scan were compared to the SD of the mean of three examinations per scan with a Mann-Whitney U test ($p = 0.793$).

Inter observer variability for the 8 eyes with edema within the 2 mm diameter circle

There was no significant difference between the mean of nine measurements made by the two observers ($p = 0.958$). We found a good correlation between the two observer's mean measurements ($r = 0.945$, $p < 0.001$). The volumetric data were then log transformed and agreement measured as before. We found good agreement as the mean differences between the two observers approached zero and the slopes of the regression lines were not significantly different from zero (Table 2).

Discussion

This paper describes the reproducibility of a new technique for the volumetric quantification of diabetic macular edema. We have previously shown that the volumes measured by this technique in diabetic patients with macular edema are statistically greater than those of age matched controls [11] indicating that the volume measured in macular edema is that of a normal macula plus an additional volume attributable to retinal thickening. The assessment area (2 mm dia. circle centred at the fovea) was chosen to provide sufficient information about the area most critical to vision. In cases of diffuse edema, the technique will tend to underestimate the volume because the reference plane is adjusted to the lowest point of the height variation of the contour line and the 2 mm circle may not include 'non thickened' retina. In such cases, the 3 dimensional map facility on the HRT enables the examiner to identify but not quantify areas of retinal thickening [11]. We do not consider this a significant disadvantage because our technique is particularly aimed at the assessment of patients with more subtle focal macular edema as the 2 mm dia. circle would be likely to include 'normal thickness' retina where the height of one sector of the contour line would be similar to the height of a normal macula.

In order to maximise the technique's reproducibility, it is essential to take good quality, well centred scans, positioning the circle which delineates the area for analysis with its centre exactly on the fovea. Ocular movement during scanning (1.6 seconds) can be detected by looking simultaneously at all 32 images taken on the monitor screen. Circle centring must be performed manually using clues obtained from the intensity image. This is more difficult when macular edema or haemorrhages are present. Despite this, we found

good agreement between scans (intra observer variability) and between the two observers' measurements of the same scans (inter observer variability).

The coefficients of variation reported for optic cup volume measurements range from 1% to 16.4% [9]. Other authors [14] assessed the reproducibility of optic nerve 'volume below contour' and 'volume below surface' in non glaucomatous volunteers. The overall CV using their data are 7.09% and 7.58% respectively. The CV of another parameter 'volume above surface' ranged from 1.9% to 6.1% [14] although this was 26% and 28.4% in healthy optic nerves and glaucomatous optic nerves in a separate study [15]. Our previous publication demonstrated an average *intra scan* CV of 8.32% and an *inter scan* CV of 20.14% for measurements of macular volumes above reference plane within a 2 mm dia. circle in 20 *normal controls* by the same technique used in the present study [12].

Zeimer et al. [4] found mean variability coefficients of 3.2% (tri-scan inter-visit), 3.6% (intra-visit) and 4.1% (single scan inter-visit) when examining the posterior pole of normal subjects with a Retinal Thickness Analyser. Spencer et al. [16] obtained variability coefficients of less than 2% in the measurement of optic disc diameters by HRT. These two studies however, analysed a two dimensional image, and in the case of Zeimer's study, only normal maculae were examined. The variability of repeated measurements of a 3 dimensional structure is much more likely to be larger than that of a 2 dimensional structure. This would account in part for the larger coefficients of variation demonstrated for optic cup volumes [9] and diabetic macular edema (the present study).

In the present study, the differences between *intra scan* CV and *inter scan* CV are attributable either to the difficulty in accurately localising the foveal centre in eyes with macular edema involving the fovea, or to the fact that different scans are not exactly identical and will therefore give slightly different volumetric measurements. We know that repeated volumetric measurements taken on smaller sized circles have larger CV indicating the sensitivity of the system to minimal displacement [11]. In practice, one might import a circle from a pre laser scan to a post laser scan, however the accuracy of such importation may not be as accurate as redrawing the circle by an experienced operator, and would therefore require a separate study. However, the relatively large CVs obtained in our study are within an acceptable range since significantly larger volumes (on average, the mean volumes in eyes with early macular edema were 244% greater than controls, with differences of up to 488% from the mean volume obtained in controls) have been demonstrated in diabetic eyes with macular edema [11]. Indeed, in the present study, the SD of repeated measurements were greater in eyes with greater volumetric measurements. In a similar vein, the variability of volumetric measurements in

this group of diabetic eyes is greater than the variability of measurements observed in normal maculae [12] as the mean volumes measured in the present study (0.206 mm^3 for all eyes and 0.260 mm^3 for edematous maculae) are much greater than the previously measured volumes in non diabetic control eyes [12]. These differences are most likely due to the increased topographic irregularity of the retinal surface in diabetic maculopathy as well as the increased difficulty in repeatedly locating the foveal centre with significant accuracy in cases of diabetic macular edema. As most diabetic eyes with no macular edema in this study had some maculopathy, the authors would therefore attribute the greater than normal volumes measured in diabetic eyes with no clinical edema to subclinical thickening not detected on fundus biomicroscopy. This appears consistent with previous findings using the RTA [1] as retinal thickening may not be detected clinically until the retina is greater than 60% thickened.

In addition, when a large volume is measured as in established macular edema, a greater measurement variation is acceptable for detection purposes, if the resulting volume differs significantly from the mean volume of a group of age matched controls. However, until the effect of laser treatment is known in such pre treatment volumes, we have to assume that the CVs of this magnitude may present a problem when assessing volume changes with treatment. Furthermore, as previous work by Shahidi et al. [17] has demonstrated up to 55% reduction in the foveal retinal thickness indices (two dimensional) after laser photocoagulation, we would expect at least similar reductions for a three dimensional measurement.

Our previous work [12] on the reproducibility of the volumetric measurements obtained in *normal maculae* showed only minimal improvement in the reproducibility when the mean of three examinations of one HRT scan is used indicating that in *normal maculae*, only one examination of one good quality scan would be a sufficient measurement. In the present study, we found a smaller average SD over 3 scans for the mean of three examinations per scan compared to one examination per scan, but the SD differences did not reach statistical significance. We would therefore recommend that the mean of three examinations of one good quality HRT scan is used when the volumes above reference plane are measured with this technique in *diabetic maculae*.

In summary, the study introduces a reliable method for the quantification of focal macular edema in diabetes with the existing software of the HRT. We recommend the use of the mean of three repeated volumes above reference plane on one good quality HRT scan. This may lead to a better understanding of the earliest changes in diabetic maculopathy as diabetic maculae with no edema on clinical examination may have above normal volumes on HRT. We are currently evaluating the role of the HRT in monitoring laser treatment and are assessing its role in screening for sight threatening maculopathy.

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Diabetic maculopathy induced by vitreo-macular traction: evaluation by optical coherence tomography (OCT)

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Abstract. *Aim:* To evaluate the role and efficacy of optical coherence tomography (OCT) in the evaluation of diabetic maculopathy induced by vitreo-retinal traction. *Methods*: 12 patients affected by diabetic maculopathy induced by vitreo-retinal traction were examined using biomicroscopy with a three-mirror contact lens, fluorescein angiography (FA) and OCT scanning in order to identify the presence of a vitreomacular traction. *Results*: OCT revealed two patterns of maculopathy which were characterised by a thickening of the superior profile of the OCT tomogram or by the disappearance and inversion of the physiologic foveal depression respectively. *Conclusions*: OCT may be useful in the characterisation and monitoring of diabetic maculopathy induced by vitreo-retinal traction.

Key words: diabetic maculopathy induced by vitreo-macular traction, Optical Coherence Tomography (OCT)

Introduction

The terms vitreous traction maculopathy, vitreous induced diabetic macular edema and maculopathy due to posterior hyaloid traction are synonymous and describe a pattern of diabetic maculopathy which is characterised by: (1) The absence of complete posterior vitreous detachment; (2) An increased retinal thickness in the center of the macula, and (3) a characteristic reflex of the vitreoretinal interface [1–4]. Associated with these changes are intraretinal microvascular abnormalities which are detectable in the macular region by fluorescein angiography. Sometimes the fluorescein angiographic picture resembles a diffuse edema but without leakage in the foveal avascular zone with a circular widespread leakage present around the hypofluorescent central area.

Because of its difficult clinical identification this kind of maculopathy is possibly underestimated. Particular care must be taken in order to detect and correctly differentiate this disease as vitrectomy with posterior hyaloid removal may represent a useful treatment.

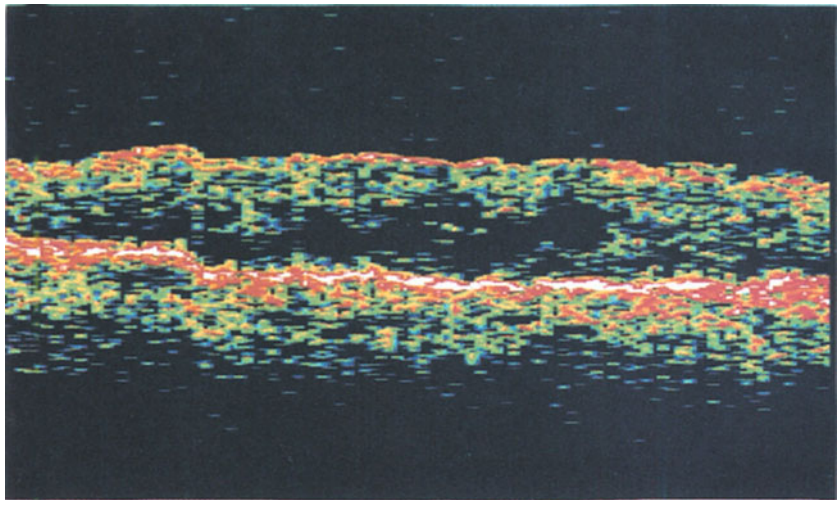

Figure 1. Preoperative foveal OCT image of a patient with Pattern 1 diabetic macular edema induced by vitreo-retinal traction (retinal thickness = 488 microns).

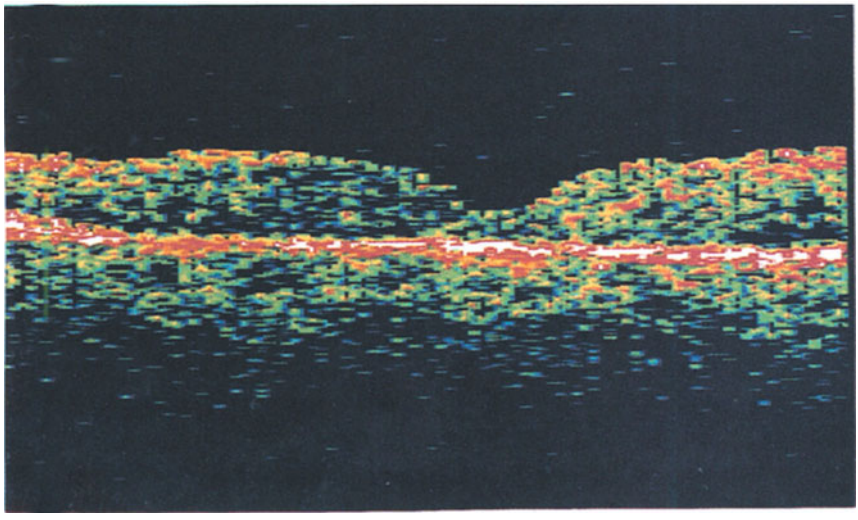

Figure 2. Postoperative foveal OCT image of the same patient as in Figure 1 showing complete restoration of the foveal pit (retinal thickness = 153 microns).

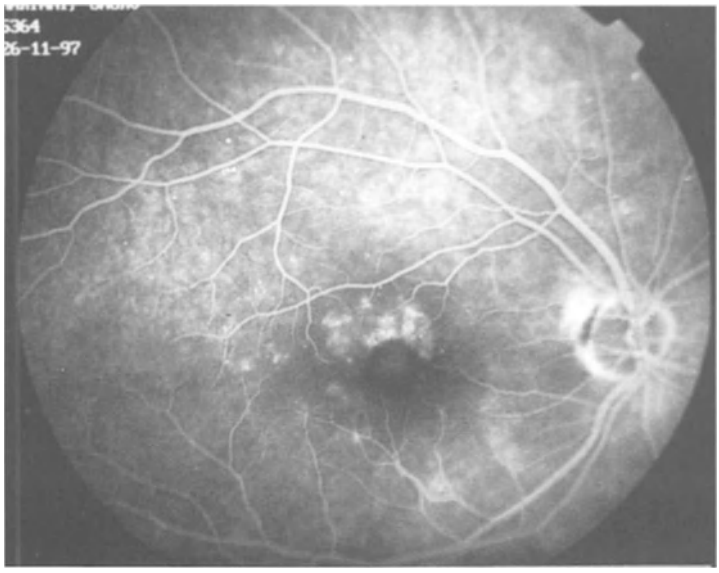

Figure 3a. Preoperative fluorescein angiograpic image of a patient with Pattern 2 diabetic macular edema induced by vitreomacular traction showing diffuse exsudation superiorly without involvement of the central foveola.

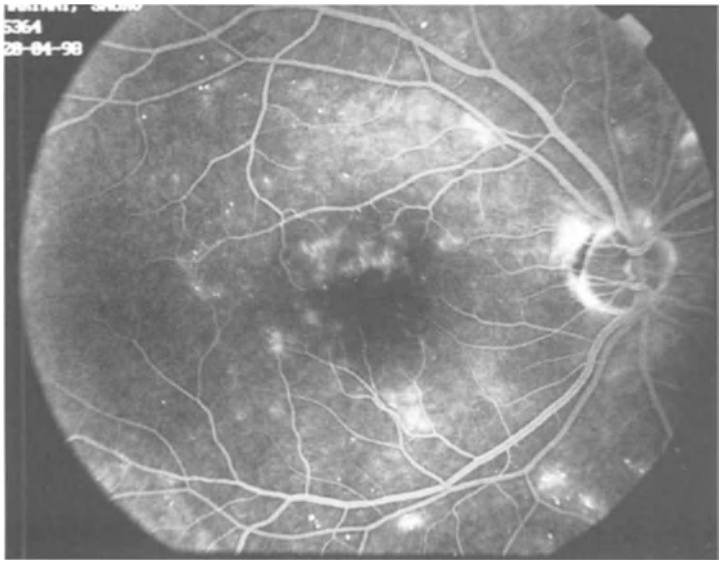

Figure 4a. Postoperative fluorescein angiograpic image of the same patient as in Figure 3 showing reduced dye leakage without involvement of the central foveola.

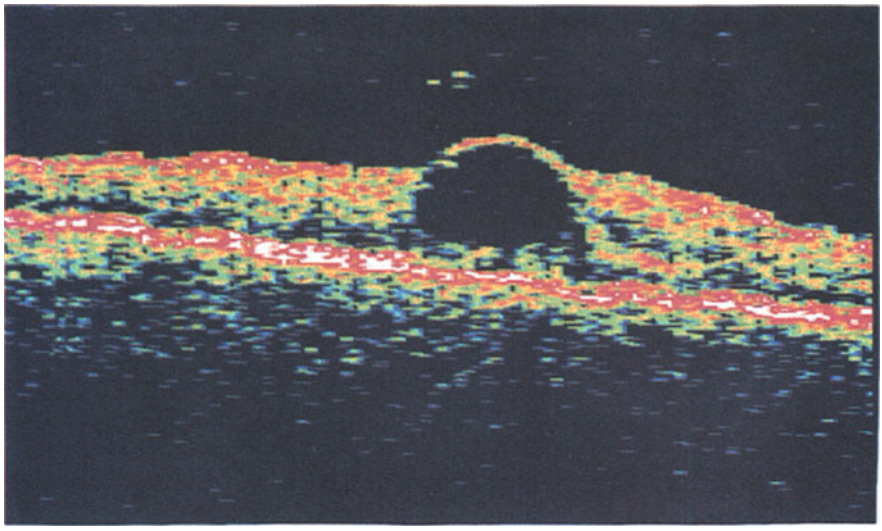

Figure 3b. Corresponding OCT image showing a large central retinal cyst which corresponds to the central black area in the fluorescein angiogram. The retinal thickness is 473microns.

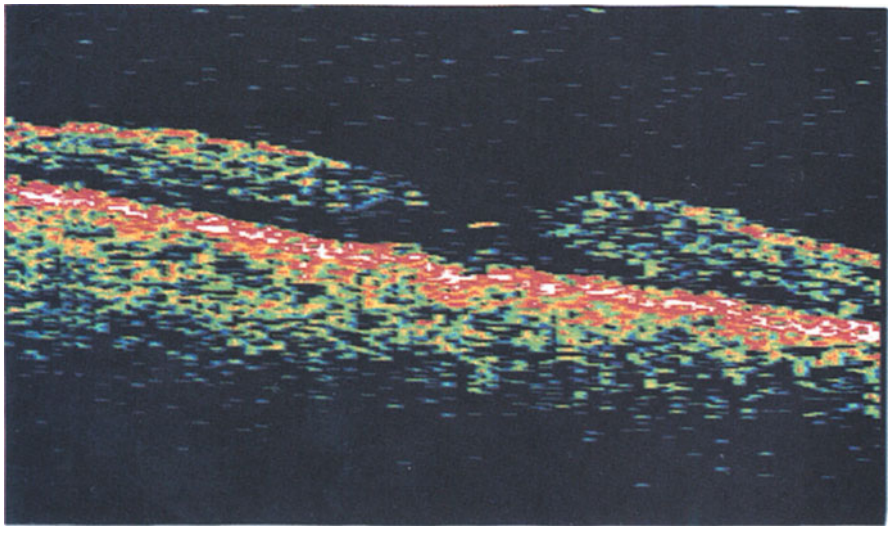

Figure 4b. Corresponding OCT image showing a restored foveal architecture with a central depression. The retinal thickness has been reduced to 145 microns.

The purpose of this study was to assess the role and efficacy of OCT imaging in the identification and evaluation of diabetic maculopathy induced by vitreo-retinal traction.

Patients and methods

We studied 12 patients with diabetic maculopathy induced by vitreo-retinal traction (18 eyes; 5 males, 7 females; age range 60–73 years). Baseline visual acuity ranged from 20/200 to 20/40. All patients underwent a complete ophthalmological examination including slitlamp biomicroscopy with a 3-mirrors contact lens, fluorescein angiography and OCT imaging (Zeiss).

Results

OCT examination revealed two image patterns which were characterised by the following appearance.

(1) Widespread, sometimes irregular thickening of the neuroretina was seen with an increased inhomogeneous reflectivity of the inner retinal structures and a disappearance of the physiological foveal profile (Figure 1). At times tractional tissue was displayed.

(2) A dome-shaped foveal area was detected which seemed to be due to a marked increase in retinal thickness. The neuroretina below the fovea was hypo or areflective and the OCT image resembled a cyst (Figure 3b).

The mean neuroretinal thickness at the fovea was 473 microns in the first group and 448 microns in the second. In all cases the foveal pit was not detectable, its profile having become horizontal in the first group, while in the second group an inverted foveal profile was present. In the first group, biomicroscopy revealed an increased reflex of the internal limiting membrane (ILM), frequently involving the whole macular region. In the second group less evident and more circumscribed alterations were present around the fovea.

Vitrectomy with removal of the posterior hyaloid was performed in 4 patients (7 eyes: 4 of the first and 3 of the second group). In 5 eyes visual acuity improved more than 2 Snellen lines, while in the remaining cases (presenting a preoperative visual acuity of $< 20/200$) vision improved less than 2 lines.

In all 7 operated eyes OCT imaging was performed 1 month after vitrectomy and showed the following results: (1) Reappearance of the normal foveal profile (Figure 2). (2) Reduction of retinal thickness (Figure 3a, b and 4, b). This finding was very marked in the 2 cases from the second group

where retinal thickness diminished from 495 microns preoperatively to 151 microns postoperatively.

Discussion

OCT appears to be able to detect alterations of retinal profile and thickness in the course of diabetic macular edema induced by vitreo-retinal traction. In all operated cases the surgical restoration of the normal foveal profile (as seen by OCT) was related to an improvement in visual acuity. In our experience OCT must therefore be considered an important tool in the diagnosis of diabetic macular edema induced by vitreo-retinal traction, as well as in the postoperative monitoring of patients with macular edema who were treated surgically.

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Optical coherence tomography (OCT) in idiopathic polypoidal choroidal vasculopathy (IPCV)

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Abstract. *Purpose:* Idiopathic polypoidal choroidal vasculopathy (IPCV) is a distinct clinical entity characterized by an edematous maculopathy and typical choroidal vascular change. The purpose of this study is to evaluate the use of optical coherence tomography (OCT) for diagnosing of this disease. *Methods:* 4 patients affected by IPVC (mean age 71–84 years) underwent biomicroscopy with a three mirror conctact lens, fluorescein angiography (FA), indocyanine green angiography (ICGA) and OCT (Humphrey Zeiss) scan. *Results:* in all 4 cases OCT tomograms acquired at the location of the typical choroidal abnormalities demonstrated by ICGA, revealed a characteristic hyper-reflectivity in the choroidal layers. *Conclusion:* ICGA is essential to diagnose IPVC, but OCT may be able to identify characteristic reflectivity patterns.

Key words: Idiopathic Polypoidal Choroidal Vasculopathy (IPCV), Optical Coherence Tomography (OCT)

Introduction

Idiopathic polypoidal choroidal vasculopathy (IPCV) is a distinct clinical entity of macular degeneration of the elderly characterized by an edematous maculopathy of acute or chronic onset. Patients affected by IPCV may present neurosensory and serous or serous/hemorrhagic detachments of the retinal pigment epithelium (RPE) [1], and the clinical picture may be confounded with that of straightforward choroidal neovascularization (CNV).

This entity was first reported by Yannuzzi in 1982 [1], and afterward described as multiple recurrent serosanguineous retinal pigment epithelial detachment [2] or as the posterior uveal bleeding syndrome [3]. The term of IPCV seems to be the most appropriate because of the unknown pathogenesis, the choroidal involvement and the characteristic spheroidal, polyplike structure of the choroidal vascular lesions. These lesions are almost always detected by ICGA. FA, on the contrary, only shows widespread leakage with clear delineation of these polypoidal lesions [4]. The purpose of our study was to identify the characteristics of OCT imaging of these choroidal lesions.

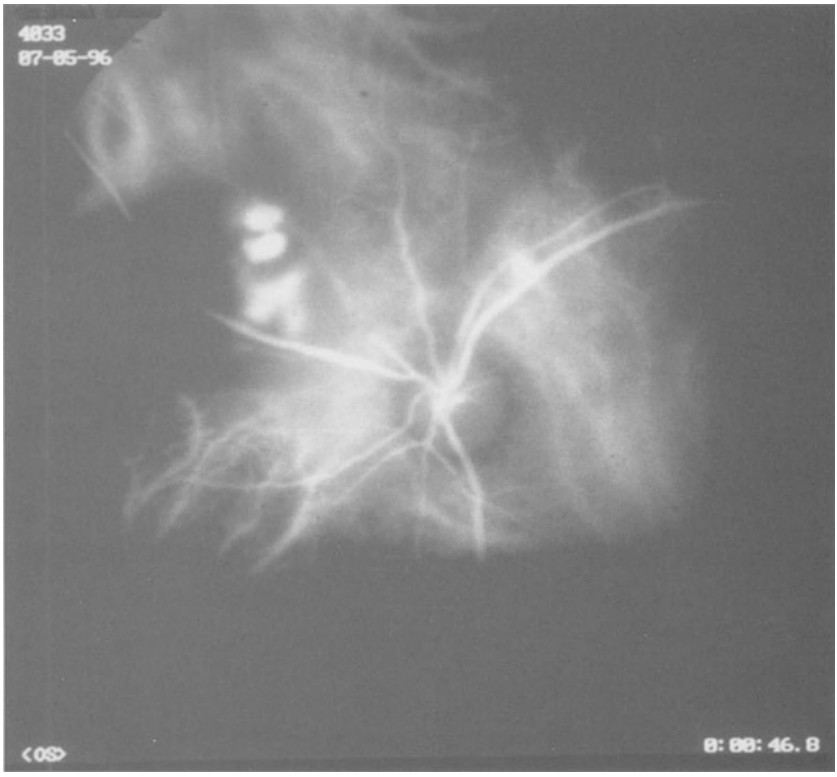

Figure 1. Early phase (46 seconds) of the indocyanine-green angiography (ICGA) in a case with idiopathic polypoidal choroidal vasculopathy (IPCV).

Material and methods

We studied 4 patients affected by IPVC (mean age 71–84 years). All of them underwent a complete ophthalmological examination, including: biomicroscopy with contact lens; fluorescein angiography (FA); indocyanine green angiography (ICG), and optical coherence tomography (OCT, Humphrey Zeiss).

Results

OCT scans acquired at the location of the typical choroidal abnormalities as previously detected by ICGA (Figures 1–2) displayed a characteristic pattern: a small elevation of the RPE, whose profile becomes dome-shaped, with an aspect similar to that of a small RPE detachment. Below the detached RPE an underlying area with reflectivity was always displayed (Figure 3). A similar

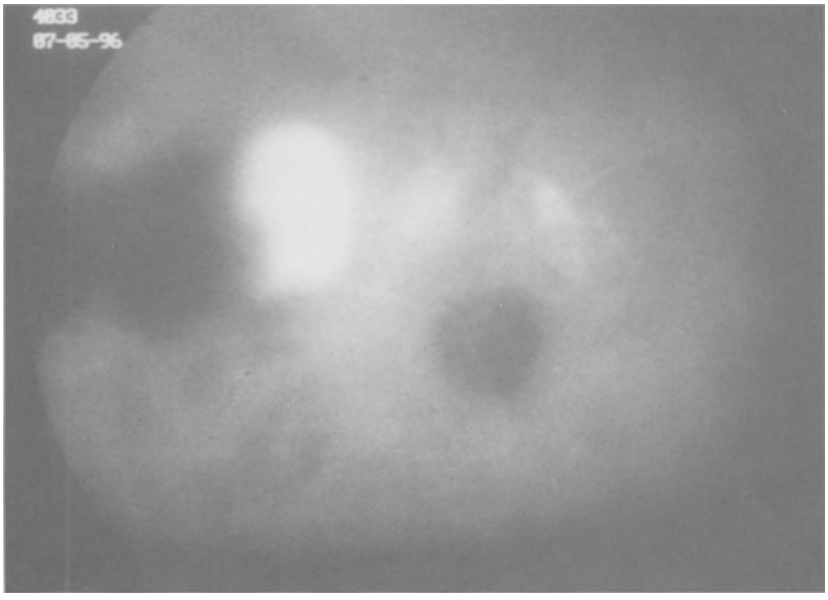

Figure 2. Late phase (20 minutes) of the indocyanine-green angiography (ICGA) in a case with idiopathic polypoidal choroidal vasculopathy (IPCV).

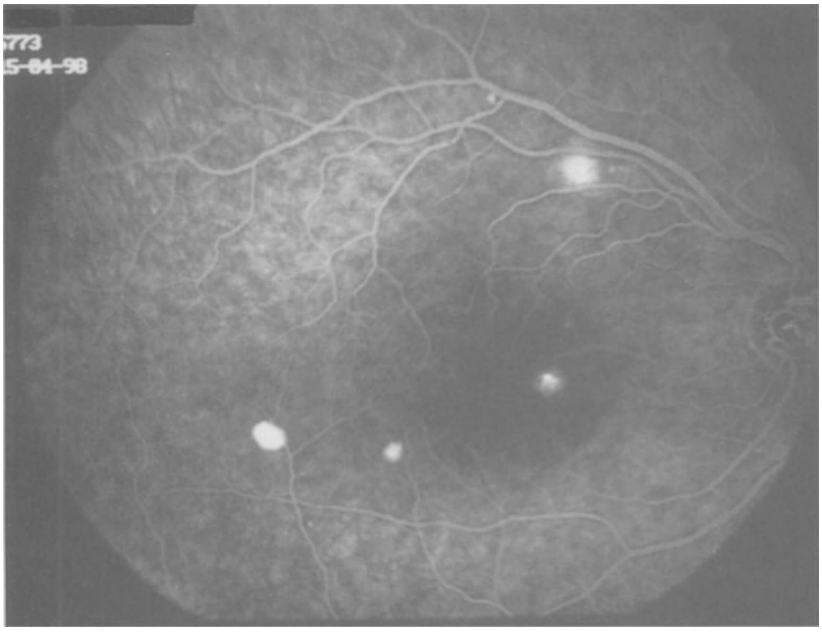

Figure 4. Midphase (2.5 minutes) of a fluorescein angiogram showing multiple small RPE detachments.

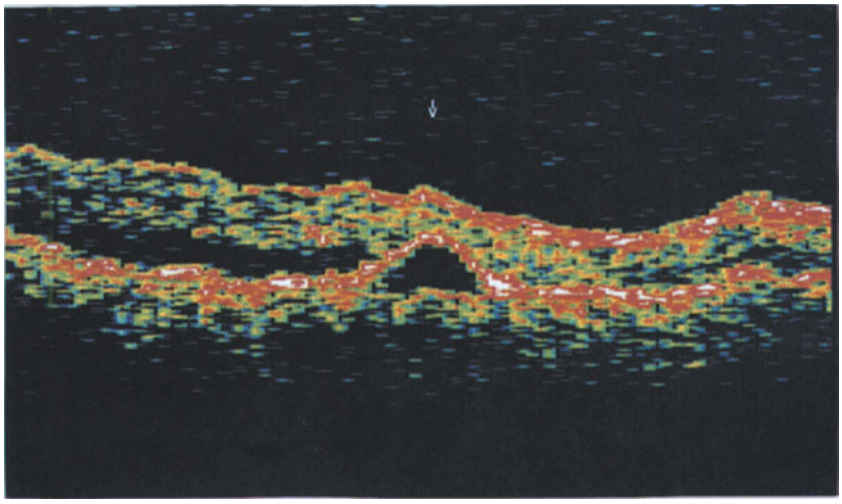

Figure 3. OCT scan acquired through the typical polypoidal lesion (small arrow) in a case with idiopathic polypoidal choroidal vasculopathy (IPCV).

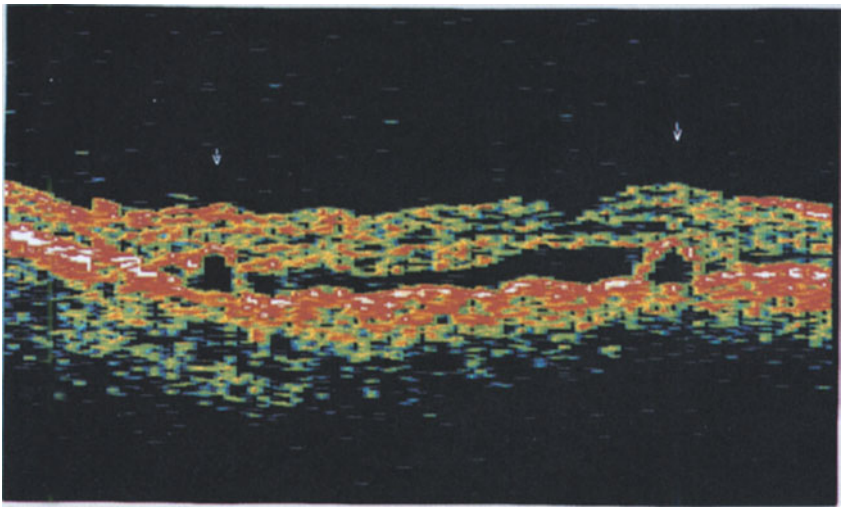

Figure 5. OCT scan acquired through two small RPE detachments (small arrows) in the same patient as Figure 4.

picture was seen in all the cases of small RPE detachments detectable in the course of various retinal disorders (Figures 4–5).

Large RPE detachments (with a diameter $\geq$ 1/2 disc diameters) always show different image such as an 'optical silence' below the detached RPE on OCT. If this is associated with a neurosensory detachment there is a non

reflective cavity with shadowing of the choroid below [5]. The pattern evoked by OCT imaging of IPCV is thus not specific of this disease, but represents a common finding in the presence of small RPE detachments. This is not surprising since Yannuzzi has hinted at the similarity of these two entities [1, 4].

Conclusions

ICGA represents the fundamental and basic diagnostic tool in the diagnosis of IPCV. Images acquired with fluorescein angiography carry the risk of misinterpretation as it only shows poorly defined lesions. The typical OCT image in the course of IPCV appears to be a dome shaped RPE detachment with reflectivity below the detached RPE without the optical silence seen in large RPE detachments. This finding is very different from that seen in the course of choroidal neovascularisation, which is usually characterized by thickening and disruption of the hyper-reflective band corresponding to the RPE/choriocapillaris complex [5]. OCT may thus be helpful in the evaluation of IPCV by complementing the data obtained by indocyanine green angiography.

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New diagnostic tools for macular edema

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Introduction

Macular edema is a leading cause of visual loss in pathologies such as diabetic retinopathy, vitreoretinal interface syndromes, ocular inflammations, branch retinal vein occlusion and cataract extraction. The pathogenetic mechanisms involve either a direct effect on macular retinal vessel permeability [1] or a secondary tangential or frontal vitreous traction. The clinical manifestation is a light greyish opacity, with an elevation of the retina sometimes evident in the affected area. When the edema persists, cystic cavities are formed especially in the outer molecular layer, the walls of which are formed by the sustenacular fibers of Muller cells. Often when the macular edema is mild, no biomicroscopic evidence is detected and a diagnosis is suggested only by an unexpected visual loss.

Currently fluorescein angiography (FAG) is the most common technique for the diagnosis of macular edema, although it only provides a qualitative assessment of vascular leakage in this pathology. FAG illustrates minute dots of fluorescence which correspond to leakages adjacent to the terminal macular vessels. In the case of macular edema the fluorescence appears only in the late phase, becoming visible after 10 – 15 min. It appears around the fovea and extends centrally and peripherally, without however quite involving the fovea itself. If the condition progresses into cyst formation at the macula, fluorescein can be seen to leak into the cysts. The edematous fluid accumulates in the outer plexiform layer of Henle over an area that is seldom more than 2 disc diameters.

Visual loss due to macular edema is also reflected by a reduction in retinal sensitivity measurable by scanning laser ophthalmoscopic (SLO) perimetry. The functional examination is more correlated to near rather than to distance vision [2]. SLO microperimetry is a new non-invasive diagnostic tool which permits an exact point to point correspondence between the fundus image and perimetric results, thus providing functional data with a direct visualization of the macular area. This technique is the most suitable device for

simultaneous fundus imaging and psychophysical testing. During SLO microperimetry stimuli of different brightness and size are projected onto the retina in real time [3]. A direct evaluation of sensitivity in a well-defined and controlled point of the macula is obtained [4].

Perhaps the most sensitive parameter which relates to macular edema associated visual loss is macular thickness. It is better correlated with edema and visual loss since an increased thickness is possible without leakage during retinal FGA [5–7]. Macular thickness is evaluated using optical coherence tomography (OCT), a new non-contact and non-invasive technique for high-resolution cross-sectional imaging of the retina [5–9]. OCT produces cross-sectional images of optical reflectivity in the retina analogous to B-scan ultrasonography with the exception that optical, rather than acoustic reflectivity of the tissue is measured with a resultant higher resolution. The OCT signal from a particular tissue layer is a combination of its reflectivity and the absorption and scattering properties of the overlying layers. Using optical interferometry to resolve distances of reflective structures within a tissue provides, under optimal conditions a resolution of 10 microns in the retina [5]. In practice precision is 10 microns in normal eyes and approximately 20 microns in patients with maculopathy from various pathologies. Measurement of retinal thickness may be obtained directly from the tomograms, either by direct manual measurement or by using computer image processing techniques. In contrast ultrasonography and scanning laser ophthalmoscopy provide a resolution of approximately 150 and 300 microns, respectively.

In the present study 28 eyes with suspected macular edema from retinal vein occlusion, cataract extraction, vitreoretinal interface syndrome, diabetes with and without retinopathy or vitrectomy for macular pucker were evaluated by FAG, OCT and SLO microperimetry in order to compare and contrast the anatomical and functional data obtained.

Patients and methods

Over a six month period (Nov. 97 to Feb. 98) FAG, OCT and SLO microperimetry were performed on 28 eyes of 27 patients affected by macular edema (16 women and 11 men, mean age 58 years, range 37–78). All patients underwent a complete ophthalmic evaluation including slit-lamp biomicroscopy, indirect ophthalmoscopy and best corrected Snellen visual acuity.

Macular edema was secondary to diabetic retinopathy in six eyes, and to diabetes without an underlying retinopathy in three eyes. The remainder of the patients presented with macular edema secondary to vitreoretinal interface syndrome (11 eyes); retinal vein occlusion (2 eyes); Irvine-Gass syndrome (5 eyes) or post-vitrectomy performed for macular pucker (1 eye).

Correlation of OCT results with those from FAG, SLO microperimetry, slit-lamp biomicroscopy and visual acuities was determined in order to detect the most sensitive technique for the assessment of macular edema.

Fluorescein angiography

Retinal FAG was performed using a Topcon IMAGEnet (SOJA TRC) angiography unit which allows a high performance image acquisition; the technique of FAG included the intravenous administration of the dye and the ensuing registering of angiographic images. This diagnostic technique is very commonly used providing only a qualitative evaluation of the dye diffusion when macular edema is present.

SLO microperimetry

Macular microperimetry was performed on all patients using a SLO (Rodenstock Inc. Munich, Germany) prototype machine coupled with microperimetry software. Two laser beams, an infrared laser diode (810–780 nm) for the retinal imaging and a Helium neon laser (730 nm) for the stimulus projection and for background illumination are used by the SLO machine. Two types of visual stimuli were used: Small flashing spots produced by a helium-neon red laser for static microperimetry and small single cross signs for fixation analysis. With this instrument stimulus intensity can be varied in 0.1 logarithmic steps from 0 to 31 dB; 0 dB (equivalent to standard value 6200 candela/m^2) represents the brightest luminance. Stimulus size was a 12×12 pixel standard (equivalent to 557.8 min of arc square, 1 corresponding to a Goldmann size III stimulus on the retina). The retinal background illumination used was 10 cd/m^2 of a helium neon laser. For fixation a single cross sign 6×6 pixel squared with a luminance of 15 cd / m^2 was used, and all tests were performed with 40 degree fields on SLO imaging. Patients were asked to fixate on the cross and signal the examiner when the test stimulus was seen. At the end of every testing session a retinal landmark such as a vessel bifurcation was selected on each image to enable the computer to calculate the real point of fixation as well as the real location of the stimulus, compensating for eye movements [3, 4].

A manual static perimetry was performed studying approximately 30 points in the macular area using a concentric grid centered on the fovea. Retinal sensitivity is expressed in decibels, converted and displayed on the monitor in an alphabetical scale (from minimal value 0 dB=A, to maximal value 25 dB=Z). The unique characteristic of microperimetry is the ability to visualize the stimuli presented on the retina in real time: this permits an accurate mon-

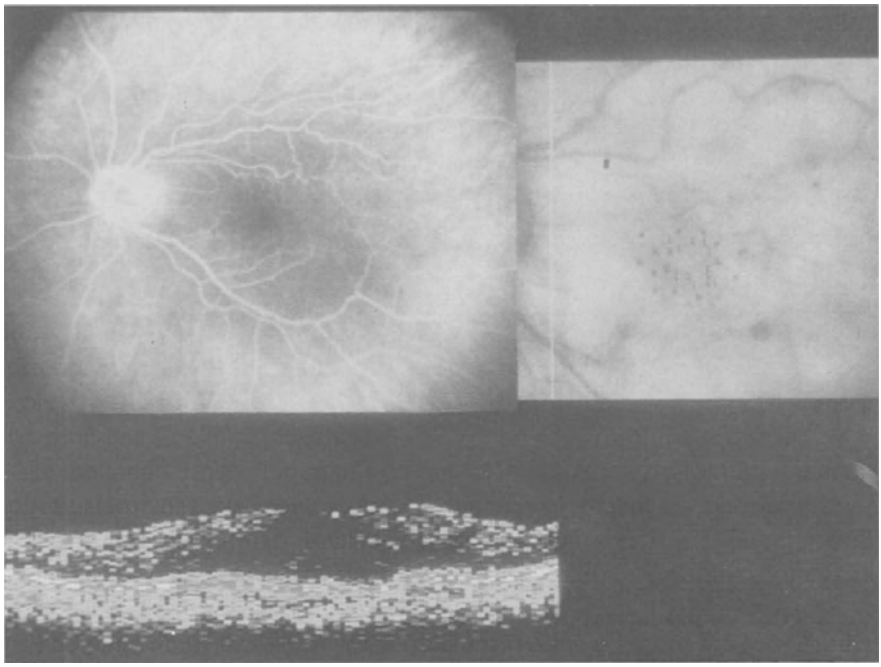

Figure 1. Top left: Fluorescein angiogram showing dye accumulation in the late phases in the perifoveal area of a patient with vitreoretinal interface syndrome. Top right: SLO microperimetry results denoting reduced retinal sensitivity in the macular area. Bottom: OCT showing extensive macular edema with thickening of the foveal retina.

itoring of fixation and permits its correlation to anatomical or pathological features directly related to retinal function [10].

Optical coherence tomography

OCT two-dimensional scans were composed of 100 A-mode scans which required a one second acquisition time [5]. The images were then processed by computer and displayed in a false color representation scale. Bright colors, red to white corresponded to regions of high relative optical reflectivity or backscattering; dim colors, blue to black, represent areas of minimal reflectivity. The mean foveal thickness was about 174±18 microns in normal eyes.

Results

Retinal FAG demonstrated the presence of macular edema in only 7 of the 28 eyes examined (25%), having visualized in these more severe cases early dye

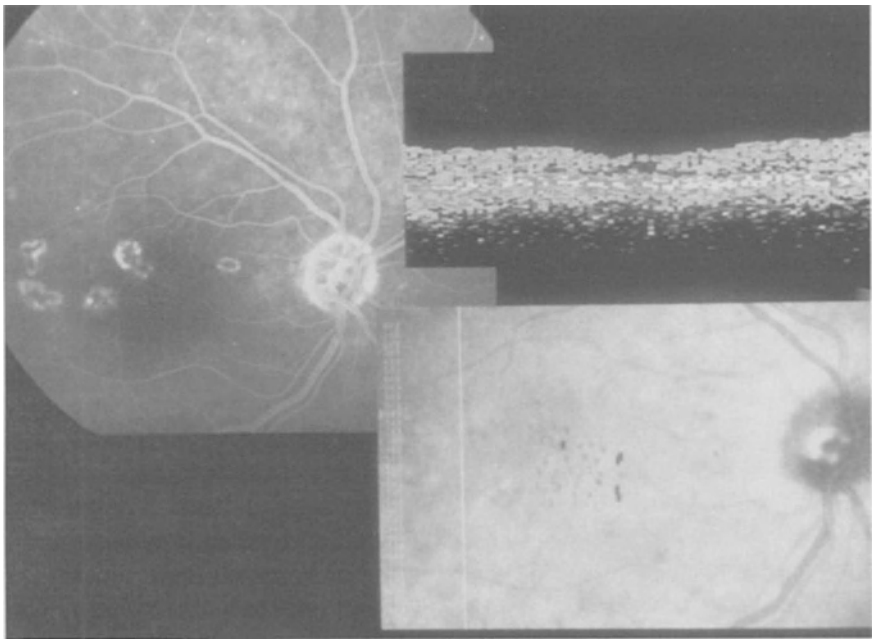

Figure 2. Top left: Fluorescein angiogram showing laser scars and very little dye accumulation in the late phases of a patient with diabetic macular edema. Right: SLO microperimetry results denoting retinal sensitivity loss in the macular area. Bottom: OCT showing hardly any fluid accumulation within the fovea.

infiltration out of the perifoveal capillary vessels and complete coloration of the intraretinal exudation.

In contrast, OCT and SLO microperimetry detected the presence of macular edema in both the 7 FAG positive cases (Figure 1) and in the 20 cases where macular edema was missed by FGA. In one eye (4%) OCT was the only technique which identified the presence of macular edema (Figure 2). Thus, retinal FAG detected macular edema in 25% of cases, SLO microperimetry in 96% of cases and OCT in 100% of cases.

OCT demonstrated abnormal signs such as a loss of the normal foveal pit contour and mild retinal thickening in all patients. When the edema was more severe (17/28 eyes; 61%), a diffuse retinal thickening, disorganization of the normal retinal architecture and a reduction of the intraretinal optical density were also evidenced by OCT. The mean foveal thickness was 180 ± 17 microns (SD) with mild macular edema, and 260 ± 105 microns in eyes with more severe macular edema. This was larger than the mean foveal thickness observed in normal eyes (174 ± 18 microns). SLO microperimetry evidenced a mild macular sensitivity reduction (about 3–6 dB) in 20 eyes (71%) and a more pronounced retinal sensitivity reduction (6–12 dB) in 7 eyes (25%).

Discussion

In all patients a reduction of two to six lines of visual acuity was present. This visual loss was coupled with a loss of retinal sensitivity as detected by SLO microperimetry in 27 of the 28 cases (96%); a mild reduction in 29 eyes (74%) and a more pronounced reduction in 7 eyes (25%). In one eye (4%) the presence of macular edema was demonstrated only by OCT and not by the other techniques. With OCT the more initial mild signs of macular edema, i.e. loss of normal foveal pit contour and limited retinal thickening were evident.

These results demonstrated the inability of ophthalmic biomicroscopy and retinal fluorangiography to detect the initial stages of macular edema. SLO microperimetry was a very sensitive functional test, the results of which paralleled vision loss, particularly near vision loss, and correlated with pathological changes in all but one patient [10].

These data confirm the OCT study of Hee and Puliafito [6, 7] in which an increase of macular thickness was present in the absence of fluorescein angiography leakage in diabetic macular edema. SLO microperimetry was shown to be better correlated to macular thickening than to fluorescein leakage, having demonstrated a reduction of retinal sensitivity in patients with macular thickening yet no visual loss.

In conclusion, OCT provided qualitative and quantitative results, visualizing both an optical density reduction and thickening of the retina. These initial changes recognized by OCT were shown to occur prior to the overt pathologic changes which lead to dye diffusion during fluorescein angiography, and thus were better correlated with the patients' otherwise unexplainable visual loss. The results of this study demonstrates that OCT appears to be the most sensitive parameter for the diagnosis of macular edema.

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Treatment of cystoid macular edema with non-steroidal anti-inflammatory drugs and corticosteroids

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Introduction

Ophthalmologists are not infrequently confronted with reduced visual acuity due to cystoid macular edema (CME). In most cases the pathology can be managed in the outpatient office. In some cases, however, a graded and systematic therapeutic approach is necessary to prevent irreversible visual loss due to fluid accumulation in the macula.

Etiology of inflammatory macular edema

The two major causes of inflammatory CME are on one side uveitis, particulary intermediate uveitis, and on the other side any postoperative intraocular inflammation. In the first situation, the inflammatory stimulus is *immunogenic* (implying multiple inflammatory mediators and complex cellular mechanisms) which act in *a continuous fashion*. A more agressive therapeutic approach is usually necessary in these situations. In the second situation the inflammatory stimulus is *traumatic* in origin (surgery, laser, chemical substances such as latanaprost) which act only during a *limited time*. The prinicipal mediators are prostaglandins and the inflammatory mechanisms are less complex (Figure 1). This type of CME responds usually very well to simple medical treatment. CME can also be found in retinitis pigmentosa [1]. More rarely, an orbital inflammation may also cause CME [2]. More recent etiologies include the treatment with latanaprost drops (Xalatan®) [3] used in the treatment of open angle glaucoma, as well as Cytomegalovirus retinitis in HIV positive patients [4].

Diagnosis

It is important to diagnose inflammatory CME without delay. Early diagnosis means early treatment which in turns is associated with a better prognosis.

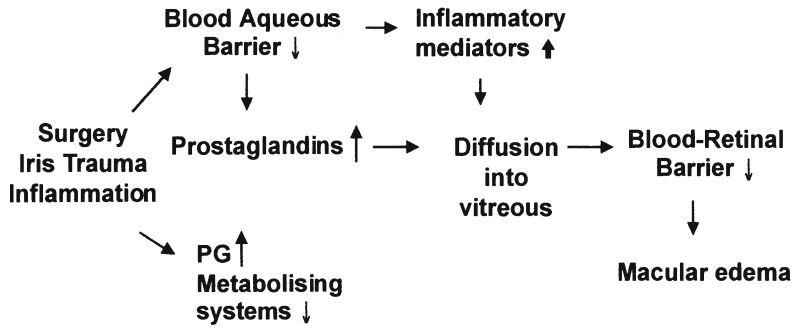

Figure 1. Effects of surgical trauma on prostaglandin production in the eye.

If the edema has developed only recently, immediate medical treatment is successful in about 90% of cases. The treatment response in chronic macular edema is less favourable and depends mainly on the retinal changes incurred due to the chronic edema.

Visual acuity loss caused by CME must be suspected in any patient followed for an inflammatory ocular disease. This may be a uveitis, a surgical inflammation or any other cause cited above. Intermediate uveitis is mostly commonly associated with CME. After cataract extraction CME is usually seen quite rapidly after the operation, although cases have been reported where the edema occurred several years after the surgery.

To allow an early diagnosis even vague subjective visual complaints of the patients must be taken seriously. These range from a haze to metamorphopsia or micropsia. The clinical diagnosis must be made by slitlamp stereoscopic fundus examination, either using a contact lens or a +90 Dpt. Lens. In cases of doubt, a fluorescein angiogram may help to discover leakage of dye in the retina, although this examination is not indicated if the clinical picture is clearcut. In some cases, fluorescein angiography is not able to detect major leakage. In these cases it may be helpful to resort to 'optical coherence tomography' (OCT) which permits to visuaise a cross section of the retina *in vivo*.

Therapeutic principles for inflammatory CME

Non-steroidal antiinflammatory drugs (NSAIDs)

This treatment should be used as a first line drug. The efficacy of topical

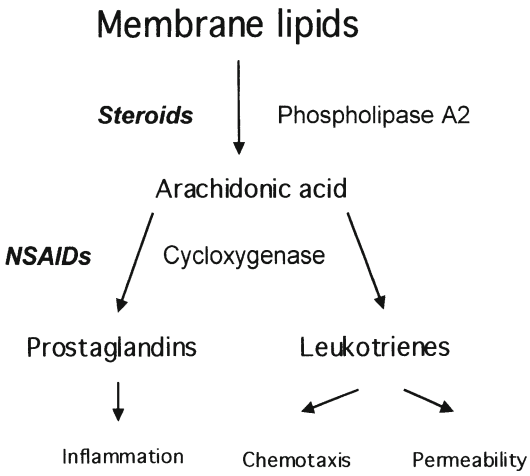

Figure 2. Site of action of NSAIDs and corticosteroids to inhibit prostaglandin and other cytokine production.

NSAIDs has been shown in several studies both for the prevention [5, 6] and the treatment [7, 8] of inflammatory CME. The action of NSAIDs is based on the inhibition of the enzyme cyclo-ogygenase which in turns inhibits the production of prostaglandins in the eye which are normally produces as a degradation product of arachidonic acid (Figure 2).

Some NSAIDs also act on other mediators. Diclofenac sodium, for example, inhibits in high doses the formation of leukotrienes which amplify cellular infiltration during an inflammatory reaction. On the basis of these findings it is thus reasonable to employ topical NSAIDs in the treatment of inflammatory CME.

Corticosteroids

The corticosteroids also inhibit the enzyme cyclo-oxygenase, but they also have a multitude of other anti-inflammatory effects by acting, among others, on interleukine-1 and by reducing vascular permeability. Their additive anti-inflammatory effect to NSAIDs was shown for the treatment of a postoperative inflammatory reaction [9]. Both these drops are used in the treatment of any inflammatory CME. Steroid treatment may also be used in association with carbonic anhydrase inhibitors [10, 11]. The mode of action is most probably the increased resportion of fluid through the retinal pigment epithelium [12, 13]. Topical Dorzolamide (Trusopt®) may also be given, although the effects are not very promising [1]. Other substances are still investigated [14].

Subtenon injection of depot corticosteroids

The periocular injection of cortison should ideally be performed as a posterior subtenon injection. This way the biggest concentration of corticosteroids will be deposited in the region of the macula. Additionally, the hypertensive effect of steroids may be avoided in the majority of cases, since the substance is not deposited in the region of the trabecular meshwork, which would be the case after a subconjunctival injection. It is important to stress that the depot corticosteroid to be used is *triamcinolone acetonide* whose solvent is not toxic for the retina (in case of inadvertent intraocular injection). Triamcinolone has even been used as an intraocular injection for the treatment of macular edema. The dose should be maintained at 40 mg of triamcinolone per subtenon injection. Treatment can be repeated 3 to 4 times after a 3 week interval. After topical anesthesia, a 25 gauge needle is introduced in the superior nasal or temporal quadrant into the subtenon space making sure that the needle is not perforating the sclera. We have performed over 450 such injections in Lausanne with no perforations. In a recent study we studied this kihave investigated the effect of sub-tenon injections in 58 eyes of 53 patients with uveitic CME [15]. A total of 162 injections were performed. Mean visual acuity increased from 0.4 to 0.8. during the follow up of 15 months. The main side effect was an increase in intraocular pressure in 27% of the cases. In 9% of patients filtration surgery had to be performed. An increase in lens opacities was noted in 12% of cases, and in two patients a ptosis of the upper eyelid was observed.

Oral or intravenous corticosteroids

The administration of oral corticosteroids is usually employed as a bolus dose in the early stages of the disease (Prednisone: 1 mg/kg per os) or intravenously (Solu-Medrolþ 500–1000 mg/day during 3–5 days). In most cases it is not the CME that makes systemic steroid treatment necessary but a generalised ocular inflammatrion which cannot be smothered by topical treatment only.

Therapeutic schematic for the treatment of inflammatory CME

In 1992 we have developed a progressive approach for the treatment of inflammatory CME (Figure 3). In the beginning we start with the least invasive therapies such as an association of topical NSAIDs and steroids 3–4 times per day. In most cases this is coupled with a systemic carbonic anhydrase inhibitors (Diamox® 250–500 mg/day) [16]. If the CME does not respond to this kind of treatment a series of 3 subtenon injections with triamcinolone are

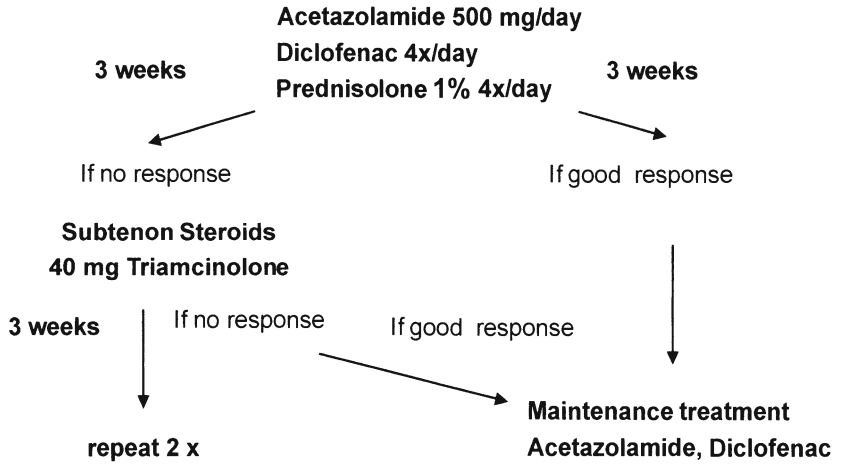

Figure 3. Schematic diagram illustrating the graded treatment approach for inflammatory macular edema.

administered (Kénacort®, Kenalog®) with a three week interval in between and discontinuation of the steroid drops. A maintenance therapy of NSAIDs and Diamox® at reduced doses (125–250 mg/d) may have to be continued indefinitely by titrating the dose according to objective and subjective observations. Using this approach more than 50% of traumatic (postoperative) CME are responding favorably. The use of subtenon injections is indicated in practically all cases of inflammatory CME. This treatment is sucessful in about 90% of non-chronic CME (< than 6 months duration).

Complicated cases – chronic CME

If chronic CME does not respond favorably to the treatment cited above, irreversible damage to the retina may have already occurred. In these cases fluorescein angiography frequently shows a hyperfluorescent colorette zone with an angiographically empty center. Using OCT, this region may reveal itself to be an encapsulated cyst which has become impermeable to fluorescein. In some cases OCT can also show retinal thickening in the inner layers of the retina with epiretinal membrane formation. These cases may be treated with vitreoretinal surgery and membrane peeling, but visual recuperation depends from the residual functionality of the retina.

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The role of carbonic anhydrase inhibitors in the management of macular edema

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Abstract. Medical treatment of cystoid macular edema (CME) with carbonic anhydrase inhibitors has been known for over a decade. Initial observations were based on experimental data which suggested that acetazolamide can increase fluid absorption across the retinal pigment epithelium. Carbonic anhydrase inhibitors (CAI) have also been shown to have other direct effects both on retinal and retinal pigment epithelial cell function by inducing an acidification of the subretinal space, a decrease of the standing potential as well as an increase in retinal adhesiveness. It is thought that acidification of the subretinal space is finally responsible for the increase in fluid resorption from the retina through the RPE into the choroid. Several clinical studies have suggested that patients with cystoid macular edema due to retinitis pigmentosa and uveitis may react more favorably to CAI treatment than other etiologies such as diabetic maculopathy or macular edema after retinal vein occlusion. The present working hypothesis is that diffuse leakage from the RPE responds more readily to CAI treatment than leakage from retinal vessels. This may be due to the modulation of membrane- bound CA IV in the RPE which may have lost its polarised distribution in the presence of macular edema. A normal clinical starting dose of CAI is 500 mg/day which should be continued for at least one month to see an effect. This dose may be reduced by the patients over the course of therapy. Metaphylaxis to the drug may occur with a rebound of the edema despite continuation of treatment.

Introduction

The carbonic anhydrase (CA) inhibitor acetazolamide has been used clinically for many years to lower intraocular pressure [1]. More recently, clinical interest has focussed on retinal disorders as an indication for this drug. Since the first report by Cox in 1988 [2], several other authors have described a positive effect of acetzolamide on the resolution of macular edema from various etiologies such as uveitis or postoperatively after cataract extraction [3], retinitis pigmentosa [4], serpiginous choroiditis [5] as well as in conjunction with epiretinal membranes [6]. The mechanisms for the reduction in macular edema with acetazolamide therapy are still not completely clear, and only a selection of patients with CME due to the mentioned underlying diseases respond favorably to treatment with CAI. A treatment regimen with CAIs may be further limited by frequent and bothersome side effects [7] which are

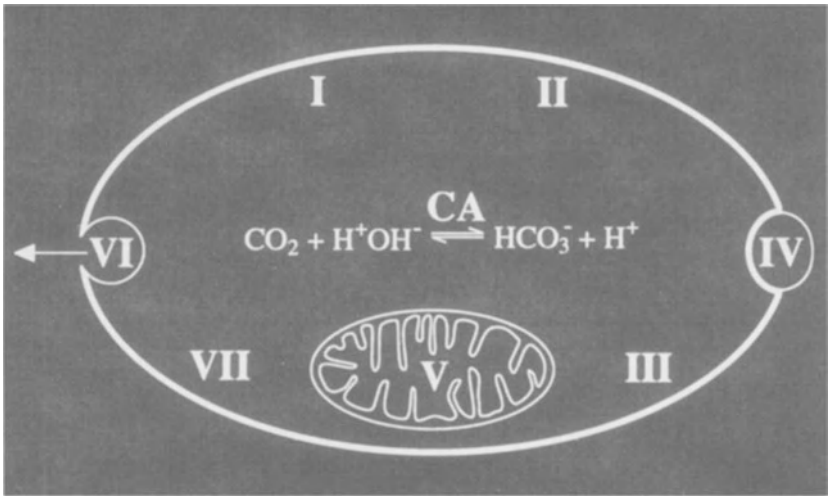


Figure 1. Schematic cell showing the different isozymes of carbonic anhydrase. The enzyme is active as a pH buffering system by catalysing the formation of water and CO_2 out of H+ and HCO_3_. The bulk of the enzyme is intracellular (CA II) whereas the membrane- bound isoform is represented by CA IV.

thought to be a result of inhibiting intracellular CA isoenzymes [8]. The clinical use of these compounds has, therefore, not become very widespread. The following review tries to amend this by showing that the clinical observations are undergirded by a large body of experimental data, and that a well informed choice of cases for this treatment can increase the chances of success.

Cellular localisation of carbonic anhydrase in the RPE-retina interface

The carbonic anhydrase enzyme is one of the most prevalent enzyme systems in our body. It occurs as several different isozymes (Figure 1) and the intracellular CA (isozyme II) represents the bulk of CA enzyme in the body being present in the erythrocytes, the gastrointestinal tract, the brain and in the ciliary body among many other tissues [9]. In the retina CA II is found in the cytoplasma of red/green cones (albeit not in rods) and especially inside Muller cells [10]. The retinal pigment epithelium, however, appears to contain almost exclusively the membrane-bound form [11]. This form of CA appears to regulate and modulate the extracellular pH gradients created by the metabolic activity of cells and may act as a bicarbonate channel [12].

CA activity in the RPE shows a clear cut polarised distribution with a large amount of enzyme on the apical surface of the cell, whereas there is less CA activity on the basolateral cell membrane (Figure 2). Further immunohis-

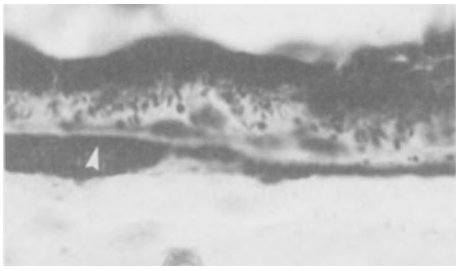


Figure 2. Carbonic anhydrase activity stain (according to Hansson) showing marked activity in the apical membrane of the human retinal pigment epithelium. There is some staining on the basolateral membrane and in the vesselwall of the choriocapillaris (small arrow). (Original magnification × 500).

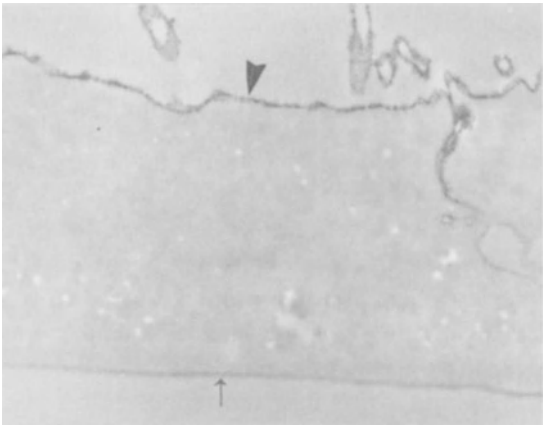


Figure 3. Transmission electronmicroscopy of a cross-section through adult cultured retinal pigment epithelial cells. Immunohistochemistry using an affinity purified *y*-globulin fraction of a chick-anti human CA IV antibody shows staining for CAIV confined to the apical surface of the cell (arrow head). The small arrow denotes the floor of the culture dish. (Original magnification × 19 000).

tochemical differentiation has shown that the isozyme IV is responsible for apical CA activity in the RPE[11] (Figure 3).

Pharmacology of carbonic anhydrase inhibitors

All commercially available CA inhibitors are unsubstituted aromatic sulfonamides, and the primary pharmacologic effects occur through reversible, non-competitive binding with the enzyme CA. The ability of a systemically applied drug to penetrate the blood-retinal barrier depends primarily on its lipid solubility, and acetazolamide, exhibiting an ether/water partition coefficient of 0.06 penetrates quite readily into the cell [13]. Benzolamide, a

more hydrophilic CAI (ether/water partition coefficient = 0.001), has also been investigated as it does *not* readily penetrate the cell membrane due to a very high degree of ionization and protein [13]. This property of benzolamide severely restricts its diffusibility across biologic membranes, and in particular across a polarized epithelial cell layer [14]. It is thus thought to act predominantly upon membrane- bound CA [15–18]. Peak drug levels of both drugs are achieved within about 4 hours.

Cellular action of carbonic anhydrase inhibitors att he RPE-retina interface

Subretinal fluid absorption

Under normal conditions in which the RPE barrier is intact, roughly 70% of subretinal fluid is removed by metabolic transport to the choroid [19]. In an *in vivo* rabbit model it could be shown, e.g. that this fluid transport (which is driven to a large extent by active ion transport through the RPE [20, 21]) can be enhanced experimentally by acetazolamide [22, 23] and benzolamide [24]. Furthermore, experiments with iatrogenically induced retinal detachments showed that the disappearance of fluorescein through the RPE increased by 25% after intravenous injection of acetazolamide [25]. The same group also observed a marked increase of resorption of subretinal fluid at a higher dosage of 50–65 mg/kg bodyweight. Further studies on the frog pigment epithelium demonstrated that active chloride and bicarbonate transport probably occurs at the basal surface which faces the choroidal blood supply [26], and it was postulated by Marmor [22] that intravenous acetazolamide reaches the basal surface more effectively. In an *in vivo* cat model it was further shown that intravenous injection of acetazolamide decreases subretinal space (SRS) volume after hypoxia-induced hydration. These findings were confirmed in the chick by using both acetazolamide and benzolamide [27].

Subretinal pH changes

Intravenous injection of acetazolamide has been shown to decrease the pH in the SRS in cat by 0.2 pH units within 45 sec [28]. This acidification was most pronounced just above the RPE and then diffused throughout the retina to the vitreous. These local changes could not be induced by creating a systemic acidosis by other means. A pH decrease could be confirmed in the chick where both acetazolamide and benzolamide induced similar changes [27]. Acidification was immediately followed by a decrease in SRS volume, and it has been postulated that the acidification may be inducing changes in ion and subsequent fluid transport through the RPE. Changes in ion flow are also reflected by a decrease of the transepithelial potential of the RPE by about 30% after intravenous injection of acetazolamide [29, 30].

Retinal adhesion

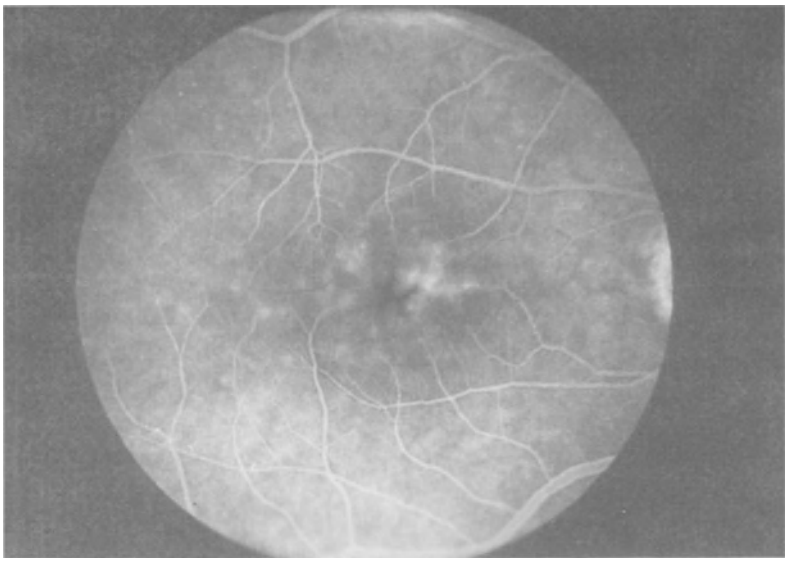
Retinal adhesion to the RPE is maintained by a variety of mechanisms [23, 31–33]. CA inhibitors probably enhance adhesiveness by enhancing RPE fluid transport. Previous studies have localised this effect to the basolateral cell membrane, since acetazolamide administered to the apical side of the RPE has had no apparent effect on retinal dahesion both *in vivo* [32, 33] and *in vitro* [23, 24], whereas intravenous injection of the drug enhanced adhesiveness [22, 32–34].

Clinical effects of carbonic anhydrase inhibitors on macular edema

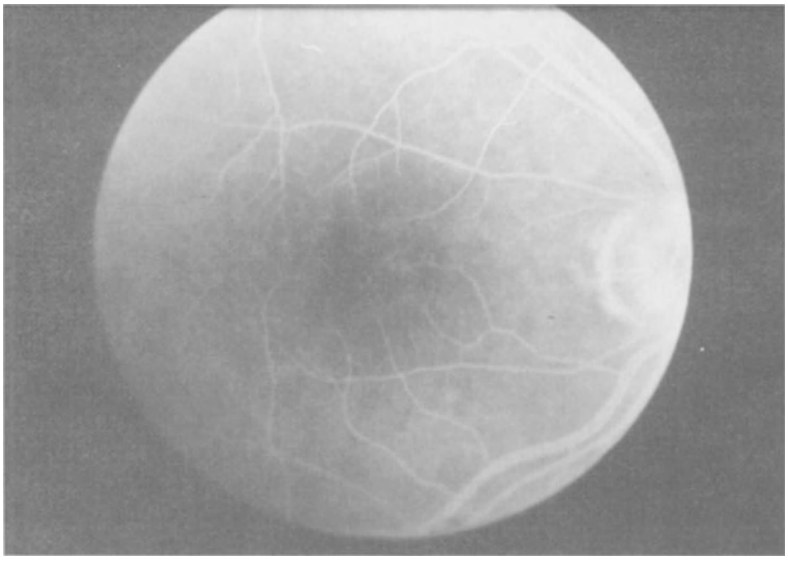
Medical treatment of cystoid macular edema (CME) with carbonic anhydrase inhibitors has been used for over a decade (Figure 4). The initial observations were reported by Cox who had prospectively studied 41 patients with CME of various causes and durations. CAI treatment was given in a cross-over fashion with 500 mg/day slow release acetazolamide sodium followed by a cross-over with another diuretic, cyclopenthiazide, which does not inhibit CA [2]. Sixteen patients showed a reproducible response to acatazolamide. The therapeutic effect occurred in more than half of patients with inherited outer retinal disease (mostly retinitis pigmentosa patients) or uveitis. Patients with CME due to primary retinal vascular disorders (diabetic maculopathy, retinal vein occlusion) did not respond well. There was no correlation between the duration of the edema and the responsiveness to treatment. No influence of the thiazide diuretic on macular edema was detected. In addition to a reduction of macular edema and an improvement in visual acuity an unexpected progressive increase in extrafoveal retinal sensitivity has also been found in RP patients with CME who were treated with CAI [5].

A similar success rate was reported in 12 patients with RP and CME, in which more than 80% of all patients improved in visual acuity after oral intake of 500 mg acetazolamide [4]. However, in this series leakage from the perifoveal vessels responded much better to CAI treatment than the leakage from the RPE. The same research group also reported rebound of CME despite continuing treatment with methazolamide in a placebo-controlled cross-over trial [35].

There have been three major studies which have investigated the effect of CAI on CME in uveitis [3, 36, 37]. Farber studied 30 patients with CME due to idiopathic chronic iridocyclitis in a prospective double-blind, placebo controlled, crossover study. There was a statistically significant improvement of visual acuity and fluorophotometry measurements after 14 days of treatment. Younger patients responded better to therapy than older individuals. Schilling et al. looked at the long-term efficacy of CAI for CME in uveitis and pseudophakia. Forty one eyes were followed-up for on average 3.1 years.



(a)



(b)

Figure 4. (a) Fluorescein angiogram showing the classical petaloid appearance of cystoid macular edema (Visual acuity 20/100). (b) The same patient after 6 months of CAI treatment. The starting dose was 500 mg which was then tapered down during the follow-up to 125 mg/day.

A 50% success rate was observed in the uveitis group, but only half of these patients could be weaned off the drug in the long run. The remaining cases needed a maintenance dosage of 125-500 mg/d for an average of 2.3 years.

Additional single case reports describing CME in association with epiretinal membranes and retinal surgery have also hinted at a positive effect of treatment with CAI [6].

The major side effects of acetazolamide treatment incurred during these trials were nausea, dizziness and paraesthesia in the arms and legs. Some patients with CME who responded well to acetazolamide were not able to continue on the drug because of these associated side effects. The inhibition of intracellular CA isoenzymes, which represent the bulk of the enzyme in the body [9], is thought to be the cause of these systemic side effects [8]. Intracellular CA may, however, not play a major role in RPE function [11]. In a recently conducted double blind placebo-controlled cross over trial looking at patients with CME due to RP, the use of benzolamide, a very ionized CA inhibitor which acts predominantly on membrane-bound CA, had indeed a similarly positive effect on visual acuity as acetazolamide but incurring less than half the amount of acetazolamide-induced side effects [38].

Another strategy to cricumvent systemic side effects of CAIs would be the direct sclero-conjunctival absorption of a topically applied CAI (Dorzolamide) into the vitreous and retina. This has been investigated in a well controlled trial assessing the effect of these drugs on macular edema in retinitis pigmentosa patients [39]. However, there was no statistically significant increase in visual acuity after several weeks of therapy, although the patients described subjectively better vision during the treatment. Whether the active agent reaches the retina by direct diffusion through the vitreous or by systemic absorption with redistribution through the blood stream is still a matter of debate.

Discussion

The exact mechanisms of the clinical effects of CAI on cystoid macular edema are still not completely clear. The present working hypothesis is that treatment response to CAI is much better in patients with diffuse RPE disease than with overt retinal vascular disease such as diabetes or retinal vein occlusions [2]. This may be due to the modulation by CAI of membrane-bound CA IV in the RPE which may have lost its polarised apical distribution in the presence of macular edema.

Leakage of fluid through the RPE has, e.g., been recorded in retinitis pigmentosa complicated by retinal edema [40]. There is also experimental evidence that pigment epithelial function is diffusely involved in cases of

both focal and generalised intraocular inflammation [41], which would include patients with uveitis and pseudophakic macular edema. It has also been suggested that RPE dysfunction occurs in retinal teleangiectasia with CME [42], which in turn may respond favorably to CAI therapy (personal observation). Further observations of CAI induced resolution of macular edema in serpiginous choroidopathy, where the pathology lies in the inner choroid and within the RPE, also undergird the working hypothesis [43]. Macular edema in disorders of retinal vasculature may simply be too extensive, and the associated morphological changes of the retina may render drainage of the intraretinal fluid impossible. Furthermore, large amounts of proteins and lipids often accompany the retinal edema in these retinopathies and fluid may be retained within the retina by a higher oncotic pressure due to these deposits.

Summary and treatment recommendations

Carbonic anhydrase inhibitors represent a useful addition to the medical treatment of macular edema. The mechanisms by which the drug enhance fluid removal are not completely clear, but may involve local changes in acid-base balance [28, 44]. Treatment success depends largely on patient selection. Patients who respond best to CAI present a type of macular edema where fluid is leaking diffusely through the retinal pigment epithelium. This may be the case in retinitis pigmentosa, uveitis, and after surgical interventions. CME in association with primary disorders of the retinal vasculature such as diabetes and retinal vein occlusions does generally not respond well to therapy with CAIs.

A normal clinical starting dose of CAIis 500 mg/d should be continued for at least one month to see an effect. Smaller doses may have to be used in children and in elderly patients. This dose may then be reduced by the patient during the course of therapy according to the subjective impression of treatment response. Metaphylaxis to the drug may occur with a rebound of the edema despite continuation of treatment. If long-term administration of CAI is envisaged, blood samples should be checked at regular intervals regarding kidney function and bone marrow suppression. A daily supplementation with KCI is advisable to counter the risk of excessive renal loss of potassium.

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Medical treatment of macular edema in patients with uveitis

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Abstract. *Purpose:* To determine the efficacy of medical treatment of cystoid macular edema (CME) in patients with uveitis. *Methods:* Retrospective study of 40 patients (57 eyes) with uveitis and CME. Inclusion criteria were presence of CME with minimal and no macular pathology, or vascular disease which could account for CME. Patients who had undergone intraocular surgery or had visual aucity (VA) of ≥20/40 were excluded. The diagnosis of CME was based on clinical and/or angiographic findings. Three treatment groups were defined: (1) transseptal injection of steroids (n=13 eyes); (2) systemic non steroidal anti-inflammatory drugs (NSAIDs) (n=11 eyes); both 1 and 2 (n=33 eyes). *Results:* Overall, 79% of eyes improved 3 or more lines of Snellen VA after treatment: 51% improved 4 or more lines. The average number of lines improved was 3.8 for eyes treated with transseptal injections of steroids, 2.9 for eyes treated with NSAIDs, and 4 for eyes treated with both. For all 3 treatment groups between 60–70% of eyes improving 2 or more lines reached best VA only after a minimum of 6 months of follow up. *Conclusions:* CME, a vision threatening complication of uveitis, respond fairly well to medical treatment; however, the best VA is achieved after several months. The improvement in VA did not differ markedly among the three treatment groups.

Key words: macular edema, uveitis

Introduction

Macular edema is by far the most common macular alteration associated with uveitis [1]. It may or may not respond to successful control of the inflammation. Almost all types of uveitis can be complicated by cystoid macular edema (CME); those most often associated with CME include pars planitis, iridocyclitis, birdshot retinochoroidopathy and sarcoidosis-associated uveitis [2]. In addition, CME is considered the most frequent cause of visual loss in many forms of endogenous uveitis [3]. Smith et al. [4], found CME in 75% of patients with intermediate uveitis having a visual acuity (VA) of 20/40 or worse.

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The optimal treatment for CME in patients with uveitis is unclear. Corticosteroids (CS), immunosuppressive agents, nonsteroidal anti-inflammatory drugs (NSAIDs) and oral acetazolamide have all been used to treat uveitic CME. However, some patients are resistant or intolerant to these treatments. Hyperbaric oxygen and surgical therapy (vitrectomy or laser photocoagulation) are still controversial.

The reasons that encouraged us to perform the study reported herein were: (1) the paucity of information in the literature about the efficacy of the use of periocular injections of corticosteroids for the treatment of CME secondary to uveitis; and (2) our understanding that oral NSAIDs, as adjuvant therapy to periocular steroids for the treatment of CME in patients with uveitis, may reduce the frequency of CME relapses. The aim of this study was to elucidate the efficacy of these two drugs for the treatment of CME associated with uveitis.

Material and methods

We reviewed the clinical records of 135 patients with CME and uveitis seen on the Immunology and Uveitis Service at the Massachusetts Eye and Ear Infirmary, Boston, during a period of 18 years (from 1977 to 1995). All clinical evaluations were performed by the same physician (CSF). The inclusion criteria for this study were: (1) Macular edema clinically and/or angiographically defined [5]; (2) Minimal or no active uveitis (<1+inflammatory cells in the anterior chamber [6], and/or vitreous lacunae); (3) VA<20/40 on Snellen chart; and (4) At least one year of follow-up. Conversely, all those patients who met the following conditions were excluded from the study: (1) Opaque media precluding evaluation of the macula; (2) History of ocular surgery inducing CME; (3) Epiretinal membrane (ERM), macular hole and ocular problems which could account for CME; and (4) Systemic conditions, such as diabetes mellitus, associated with macular edema.

Once included in the study, the patients were divided into three groups according to the treatment received for their CME: (A) Regional injections of corticosteroids (RCS); (B) Systemic NSAIDs; and (C) Both treatments (RCS+NSAIDs). RCS were performed with 40 mg triamcinolone acetate (1 cc) mixed with 2% lidocaine (0.5 cc), administered through a 0.5 inch 30 gauge needle through the inferior preorbital septum. Patients underwent a complete ocular examination at each visit, including: best corrected visual acuity as Snellen equivalent, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement and dilated funduscopy. All patients were investigated initially with a careful review of all organ systems and laboratory studies in order to reach a diagnosis for the uveitis cause. The laboratory investigations

were individualized for each patient based on the suspected diagnosis. The uveitis was classified according to the recommendations of the International Uveitis Study Group [7]. Data harvested from the clinical records included those related to the uveitis (diagnosis, localization, course, duration, treatment and follow-up) and those related to the episode/s of CME (number of episodes of CME, duration of each episode, treatment for CME and secondary untoward effects, time free of CME between episodes, VA before, during and after treatment of CME, IOP before and after treatment of CME, secondary complications of the macular edema itself and number, duration, intensity and treatment of the flare-ups of the uveitis between CME episodes). Two groups were considered regarding the duration of each episode of CME: one group with a CME duration of less than 6 months and a second group for a CME duration of more than or equal to 6 months. The criterion for 'improvement' was an increase of at least two lines of Snellen visual acuity.

Results

Characteristics of the patients

Characteristics of the study patients and descriptive data for uveitis are presented on Table 1. A total of 40 patients (57 eyes) fulfilled the criteria for inclusion on this study. Twenty-two (55%) patients were male, 19 (98%) were white, and the mean age was 40 years (range: 9 to 68 years). Fourteen eyes (25%) had acute recurrent uveitis, while the uveitis was chronic in 43 (75%) eyes. Intermediate uveitis was most common (25 [40%] of 57 eyes), followed by anterior uveitis (15 [26%] of 57 eyes). The most common diagnoses (Table 2) were idiopathic uveitis (19 [33%] of 57 eyes) and pars planitis (9 [16%] of 57 eyes). The average follow-up time was 56.5 months (range from 12 to 166 months).

CME

The diagnosis of CME was established by fluorescein angiography in 33 (58%) eyes, and by clinical criteria in 24 (42%). The duration of the first episode of CME was less than six months in 24 (42%) eyes, and greater than six months in 33 (58%).

Medical treatment for CME

Treatment of the first episode of CME was as follows: 13 (23%) eyes received RCS injections alone, 11 (19%) eyes received NSAIDs alone, and 33

Table 1. Demographics

	Patients (No.) n=40	Eyes (%) n=57
Sex		
Female	21	31 (54)
Male	19	26 (46)
Age		
<30 years	10	16 (28)
30–45 years	15	22 (39)
>45 years	15	19 (33)
Course of uveitis		
Acute	12	14 (25)
Chronic	28	43 (75)
Type of uveitis		
Granulomatous	1	1 (2)
Non Granulomatous	39	56 (98)
Location		
Anterior uveitis	12	15 (26)
Intermediate uveitis	14	23 (40)
Posterior uveitis	9	13 (23)
Pan uveitis	5	6 (11)
CME duration[a]		
<6 months		24 (42)
≥6 months		33 (58)
Uveitis duration		
<5 years	14	20 (35)
5–10 years	13	21 (37)
>10 years	13	16 (28)

[a]The number of patients is not listed given the variable behavior of the CME by eye even when affecting bilaterally same patient.

Table 2. Diagnosis

Diagnosis	Patients (No.)	Eyes (No.)	Eyes (%)
Pars Planitis	6	9	15.7
Sarcoidosis[a]	5	6	10.5
Birdshot retinochoroidopathy[b]	4	6	10.5
HLA-B27+associated uveitis[c]	5	5	8.7
JRA	3	4	7.0
SLE suspected	1	2	3.5
Inflammatory bowel disease	1	2	3.5
Behçet disease	1	2	3.5
Wegener's Granulomatosis	1	1	1.7
Reiter's syndrome	1	1	1.7

JRA: Juvenile rheumatoid arthritis; SLE: Systemic lupus erythematosus; [a]Two patients had the diagnosis of Presumed Sarcoidosis. [b]One patient had the diagnosis of Birdshot vs. Epstein-Barr Virus. [c]One patient (one eye) had Ankylosing spondylitis. One patient (one eye) had Ankylosing spondilitis and Ulcerative colitis.

Table 3. Time required to achieve the best post-treatment VA

	6 months (% of eyes)	12 months (% of eyes)
≥2 lines of Snellen VA		
RCS	70	30
NSAIDs	75	25
RCS+NSAIDs	78	22
≥4 lines of Snellen VA		
RCS	63	37
NSAIDs	67	33
RCS+NSAIDs	78	22

(58%) eyes received both RCS and NSAIDs therapy. In 9 (16%) eyes, the CME was additionally treated with Carbonic Anhydrase Inhibitors (CAI). Systemic treatment for CME was discontinued in three patients due to side effects (sleep disturbances, gastric ulcer, and stomach upset respectively).

The average number of injections administered was 1.3 per patient per minimum follow-up of 1 year.

Visual acuity results

Overall, 79% of eyes improved two or more lines of Snellen VA following treatment during the first CME episode; 51% improved four or more lines. For all the three groups, between 60–70% of eyes improving two or more lines reached best VA only after a minimum of six months of follow-up (Table 3).

To evaluate the relative efficacy of treatment, we compared Snellen VA before and after the episode/s of CME for patients in the three treatment groups. For patients with two affected eyes, data for the two eyes were averaged. Results indicated no statistically significant difference in the mean number of lines improved for the three treatment groups. Patients treated with RCS injections of steroids showed an improvement of 3.8 lines, compared to 2.8 lines of improvement for patients treated with oral NSAIDs, and 4.0 lines for patients treated with both.

Eyes with multiple episodes of CME

Fifteen (26%) of the 57 eyes had more than one CME episode. For 9 (60%) of these eyes, the second episode of CME was preceded by a flare-up of the uveitis. Nine (60%) of the 15 eyes showed an improvement of two or more lines of Snellen VA after treatment, and 6 eyes improved 4 or more lines.

The development of ERM was more common in eyes that experienced multiple episodes of CME; 6 (40%) of 15 eyes with multiples episodes developed ERM compared to 8 (19%) of 42 eyes with a single episode of CME.

Statistical analysis

The Kruskal-Wallis test was used to analyze the statistical significance of the differences between number of lines improved.

Discussion

CME in patients with uveitis is a relevant problem because of its frequency and its influence on final vision. Numerous aspects of this macular alteration still remain unknown. Pathogenesis, best treatment, and correlation between presence of CME and VA are unclear. Fluorescein angiograms show that capillaries in the macula and optic disc are preferentially affected in patients with CME, while capillaries in other parts of the retina are not. Typical fluorescein leakage and accumulation still remains the accepted mode to demonstrate the presence of CME, but further studies have indicated a

poor correlation between leakage on angiography and visual acuity [8, 9]. It has been suggested that macular thickening correlates better with visual loss than does macular leakage, as determined by fluorescein angiography, at least in patients with uveitis and macular edema. Optical coherence tomography could be a useful tool for objectively monitoring retinal thickness in patients with CME [10].

Today, there is no accepted treatment modality for CME secondary to uveitis. Both human and experimental evidence suggests that inflammatory mediators cause the perifoveal leakage that occurs in CME secondary to uveitis. It is for this reason that corticosteroids have been used to treat CME. Experimental studies have clearly demonstrated that posterior periocular injections of corticosteroids produce higher steroid levels in the posterior segment of the eye than do systemic steroids, particularly when the eye is inflamed [11, 12]. This, in combination with the lower risk of systemic side effects, has made periocular injections of corticosteroids the predominant therapy for management of CME. Five of six eyes (83%) that had failed to respond to systemic corticosteroids responded to regional corticosteroids injections in the study reported by Riordan-Eva and colleagues [13]. However, there is still the potential for local side effects, including globe perforation. Few clinical studies to elucidate the efficacy of periocular injections of corticosteroids for the treatment of CME secondary to uveitis have been performed. Similarly, almost no studies of the efficacy of NSAIDs therapy for CME have been reported, despite the fact that prostaglandins have been implicated in the generation of persistent uveitic CME.

We found an improvement of two or more lines of Snellen VA for 79% of the eyes (51% improved four or more lines) independently of the treatment received. Jennings et al. [9] studied the effect of posterior sub-Tenon's injection of corticosteroids in 12 eyes with CME secondary to uveitis; 50% of the eyes had an improvement in VA (two lines on the Snellen chart) which lasted at least for 4 weeks. More recently, the group of Yoshikawa [14] reported the results of their study in which posterior subtenon's injections of corticosteroids improved VA (two or more lines) in 56% of the eyes after a follow-up of 6 months; the number of injections per eye ranged between 2 and 7.

Thirteen eyes of our study received RCS as treatment of CME; 77% of them improved >2 lines of VA. Eleven of those 13 eyes were on systemic treatment for the uveitis. For nine of them (69%), the systemic treatment was oral NSAIDs. Additionally, 70% of the eyes with improving VA after being treated with RCS for CME were on NSAIDs as treatment for their uveitis. NSAIDs therapy, in conjunction with topical, periocular, or systemic steroids constitute an important facet of our approach to the management of patients with uveitis. Specifically, these agents are steroid-sparing and our results sug-

gest that systemic NSAIDs may be a useful adjunct to regional corticosteroids for the treatment of CME associated with intraocular inflammation.

Seventy per cent of eyes with CME duration greater than or equal to 6 months improved two or more lines of VA. Improvement in vision for eyes with CME episodes shorter than 6 months was found in 90% of the eyes. Yoshikawa [14] and colleagues underlined the importance of treating CME at an early stage. In their study, eyes showing better responses were those with a better pretreatment VA.

Nine eyes included in our study required additional treatment with CAI. Acetazolamide may be beneficial in treatment of CME related to inflammation but recurrence of edema necessitating resumption of previously discontinued acetazolamide has also been reported [2]. In agreement with Whitcup [15] we believe that acetazolamide should be reserved for chronic uveitis-associated CME unresponsive to other treatment strategies. Accordingly, we used acetazolamide for a group of patients with chronic CME that failed to improve with other treatments. All of them had a single episode of recalcitrant CME except for one eye. It is unclear why CME was so persistent in these eyes. To address this question a longer follow-up of this patients could be required.

CME, a vision-threatening complication of uveitis, seems to respond reasonably well to medical treatment. The improvement in VA does not significantly differ among the three treatment groups, but the best VA was achieved after several months of treatment. Ophthalmologists involved in caring of patients with uveitis should assume that control of inflammation might be a long process. VA improvement appeared to be more common in cases of CME with duration less than 6 months in comparison with CME duration more or equal to 6 months.

Our study is an example of how successful control of the inflammation in a patient with uveitis may not parallel the resolution of CME. Uveitis was inactive or with minimal inflammation in all the patients who were selected for the study. The limitations of our study should be taken into account; it is retrospective in nature and it lacks methods to objectively quantify the effect of the treatment on CME. Nonetheless, we believe that the observations reported herein highlight the need for a prospective study on this subject.

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Treatment of uveitic macular edema with acetazolamide

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Introduction

Visual impairment in chronic uveitis may be the result of band keratopathy, cataract formation, vitreous haze, secondary glaucoma or optic nerve involvement. However, the main reason for severe visual impairment in uveitis is chronic cystoid macular edema [6]. The often unsatisfactory treatment of macular edema with corticosteroids stressed the need to find new therapeutic concepts [2]. Although experimental studies have shown that acetazolamide improves fluid absorption through the retinal pigment epithelium (RPE) by inhibiting carbonic anhydrase subtypes (and probably other enzyme systems) [4, 8] so far only a few clinical studies have investigated the value of acetazolamide on uveitic macular edema [1, 3, 5, 7]. The results were inconsistent: while some investigators found an effect on visual acuity, others did not.

However, a lot of differences between these studies exist. The initial dosage was not standardised and the follow up time was limited to several weeks in most cases. Experiences are thus currently limited with regard to initial and maintenance dosage for the long-term use and to the long-term effect of acetazolamide on visual acuity.We have found 250 mg acetazolamide given twice daily of help in several of our patients with recurrent uveitic macular edema if given in addition to the antiinflammatory treatment.

The aim of this study was to investigate the effect of acetazolamide on visual acuity under the following conditions: (1) Slow and individual reduction of acetazolamide. (2) Individual maintenance dosage. (3) Differentiation between acute (< 2 months duration) and chronic(> 2 months duration) macular edema.

Patients and methods

Thirty patients with endogenous uveitis associated with clinical macular edema were enrolled in a non-controlled and open study between 1996 and

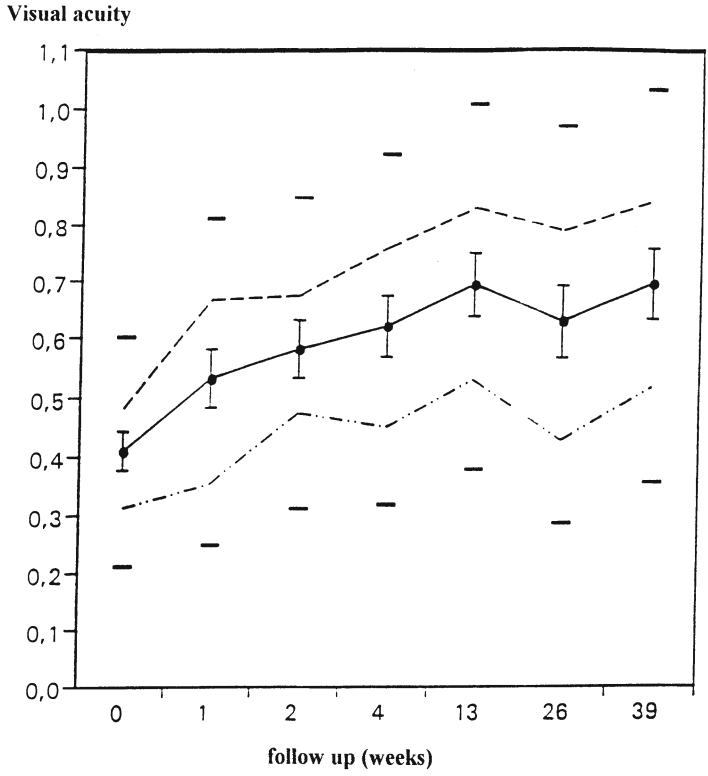

Figure 1. Effect of acetazolamide therapy on the visual acuity [median visual acuity ± standard deviation (error range)] over a period of 9 months in 29 of 30 patients (—). Improvement of visual acuity was statistically significant (p = 0.0005). Macular edema was present less than two months in 16 patients (- - - -), and more than two months in 13 patients (- .. -). The difference of the median visual acuity between both groups was statistically significant (p = 0.0001).

1997. All patients received initially acetazolamide 250 mg twice a day (except three children who received half that dose). Depending on the effect of the treatment on visual acuity and the activity of the macular edema there was a stepwise reduction of the dose (by decrements of 60–125 mg) every 3 to 4 weeks. Every patient received a substitution of potassium during the treatment. A complete blood cell count and blood chemistry was performed for each patient every 4 to 6 weeks. Visual acuity was recorded over a follow up period of 9 months. Data analysis was performed on two subgroups: Patients with macular edema of less than 2 months and patients with macular edema of more than 2 months duration. The topical antiinflammatory treatment was continued during the observation period. Statistical analysis was performed by using the paired student t-test and by analysis of variance.

Table 1. Patients characteristics, types of uveitis and antiinflammatory medication

Sex	
Females	17
Males	13
Age (yrs)	
Mean	34.5
Range	8–62
Type of uveitis	
Anterior	8
Idiopathic	3
HLA-B27 associated	3
(one case with ankylosing spondylitis)	
JCA	1
Sarcoidosis	1
Intermediate	19
Idiopathic	16
Sarcoidosis	2
Multiple sclerosis	1
Posterior (idiopathic)	1
Panuveitis	2
Idiopathic	1
Behcet's disease	1
Antiinflammatory medication	
Only topical medication	7
Systemic corticosteroids	17
Immunosuppressive agents	6

Results

Visual acuity

Visual acuity was followed over a period of 9 months in 29 of the 30 patients, and it could be observed that vision increased slowly during the follow-up period (Figure 1). The mean increase of visual acuity was 0.29 lines (95% confidence interval 0.17:0.40). This increase was statistically signific-

ant (p=0.0005). Visual acuity increased two or more lines in 17 out of 29 eyes (59%). Therapy was more effective in macular edema persisting less than two months (acute macular edema). In this group visual acuity increased two or more lines in 12 out of 17 eyes (71%) within 9 months. In eyes where macular edema had been present for more than two months (13 eyes), visual acuity increased only in 38% by two or more lines.

Dosage

A maintenance dosage of acetazolamide was still necessary in 16 patients after 9 months of observation: Visual acuity decreased immediately in 9 patients after reduction of acetazolamide therapy, which was thus quickly reinstituted. In 7 patients macular edema recurred later and therapy was also resumed. The complete withdrawal of treatment during the 9 month follow up was successful in 8 patients without recurrence of clinically significant macular edema. In 5 patients the treatment was abandonned because no effect on visual acuity was observed.

Side effects

Medication was discontinued in one patient and reduced in three patients because of intolerable gastrointestinal side effects. After dose reduction continued therapy was tolerated in the latter cases. No changes in the laboratory workup were found in any of the patients during the follow up.

Discussion

The results of our study suggest that acetazolamide – if given in addition to antiinflammatory drugs – is effective in treating uveitic macular edema. An initial dosage of 250 mg twice daily was given and a stepwise and individual reduction of therapy depending on the visual acuity was undertaken. The initial dosage appears to be sufficient and the increase in visual acuity was statistically significant after 9 months of observation. To our knowledge, this represents the longest follow-up of uveitic macular edema treated with acetazolamide. However, our study harbors some limitations. There was no control group, different subtypes of uveitis were treated and the concurrent use of different antiinflammatory treatments may have unduly influenced the treatment effects.

As it was reported by other authors there is a high preponderance for recurrence after reduction the acetazolamide dose [1, 3, 7]. In our study, an individual maintenance dosage was necessary in more than half the patients

to retain a therapeutic effect even after 9 months of follow up. As reported before, some patients suffered from gastrointestinal side effects which hampered the treatment. However, the positive effect was only absent in one patient who had to completely abandon the treatment.

It appears from our data that acetazolamide is more effective in acute than in chronic macular edema. This may be due to irreparable neural changes that occur as the result of longstanding diffuse edema.

We conclude from the present data, that acetazolamide may be a useful second line medication to support the antiinflammatory treatment, which remains the mainstay of uveitic macular edema therapy. More extended studies are needed to gain further insights in the action of carbonic anhydrase inhibitors in the treatment of macular edema.

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When and how to do a grid laser for diabetic macular edema

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Abstract. Macular edema is a common feature of posterior segment diseases. It is an expression of abnormal permeability in either retinal vessels (inner blood-retinal barrier) or in the retinal pigment epithelium (outer blood-retinal barrier). It occurs in either a diffuse pattern where the macula appears generally thickened or, in more severe cases, as cystoid edema with the typical petaloid appearance. Grid laser treatment may be useful to reduce macular edema. Spots of 100–250 micrometers in diameter are applied to the whole posterior pole, one to two groups apart. The foveal avascular zone remains untouched. In patients treated bilaterally, areas temporal and nasal to the macula must be spared to prevent the development of deep scotomas. The mechanism yielding positive results with the grid technique is still debated. Among the most reliable hypotheses are: Proliferation of pigment epithelial cells, followed by and improved efficiency of the outer blood-retinal barrier; proliferation of endothelial cells in retinal capillaries followed by an improved efficiency of the inner blood-retinal barrier; improvement of the retinochoroidal exchanges, and finally, release by coagulative necrosis of a factor able to improve the efficiency of the blood-retinal barriers. Lasers with long wavelengths, such as krypton red and diode, are the most appropriate ones to perform grid treatment.

Key words: grid laser treatment, krypton, diode laser

Introduction

The extracellular space of the retina normally constitutes a small proportion of the retina's total volume. With disruption of either the inner or outer blood-retinal barrier, increased entry of constituents of the plasma and water allows a significant expansion of the extracellular space of the retina. The increase in water content of the retinal tissues may also be intracellular initially. This site of toxic edema is secondary to an alteration of the cell ionic exchanges with an excess of intracellular Na+. [1, 2].

A summary of diseases associated with macular edema was published by Morton Goldberg [3], and modified by Lee Jampol [4]. The list includes metabolic diseases, ischemic diseases, mechanical disruption, hydrostatic forces, inflammation, hereditary diseases and toxic conditions.

Indications for laser treatement

Laser treatment is indicated when the cause of macular edema is secondary to vasculopathies, such as diabetes mellitus, vein occlusion or retinal angiomatosis. There is no proven indication for laser treatment when the cause of macular edema is inflammation or epiretinal membranes.

The Early Treatment Diabetic Retinopathy Study (ETDRS) [5] has demonstrated the value of laser treatment in preventing or reversing visual loss from diabetic macular edema. Reduction of visual acuity by two lines occurred in 24% of untreated eyes versus 12% of the treated one. We must underline that for a correct interpretation and for a transferability of ETDRS results, it is essential to use the same grading system classification employed in the ETDRS trial. The ETDRS defined the diagnosis of clinically significant macular edema on the basis of biomicroscopic or stereo photograph evaluation of the fundus [5, 6]. In many European countries this grading system is not usually employed because patient evaluation and treatment choice is generally based on a fluorescein angiogram.

This different attitude originates from the better quality of information that we can obtain from the early and late fluorescein frames. By this way it is possible to evaluate a macular capillaropathy responsible for retinal thickening, and the condition necessary to perform a causal laser treatment can be achieved. On early fluorescein angiograms microvascular abnormalities are well defined and on the late ones the leakage is evident. For these reasons retinal fluorescein angiography is the most reliable diagnostic technique to identify microvascular abnormalities responsible for the edema and the hard exudates. On the contrary, biomicroscopic examination, however carefully done, allows to evaluate only the consequences and seldom the cause of retinal lesions. Fluorescein angiography, therefore, turns out to be a mandatory requirement for early and well-grounded laser treatment.

In the ETDRS protocol, discrete areas of leakage were treated with focal laser, and areas of nonperfusion or diffuse leakage associated with macular edema were treated with grid treatment. Therefore it is still debated whether focal therapy is better than grid laser treatment. In other words, which of the two techniques is better to use? We tried to answer this question by performing a study in which 60 eyes affected by diabetic macular edema were randomly assigned to focal or to grid treatment. After 2 years of follow-up, visual acuity and ophthalmoscopic appearance were comparable in the two groups [7].

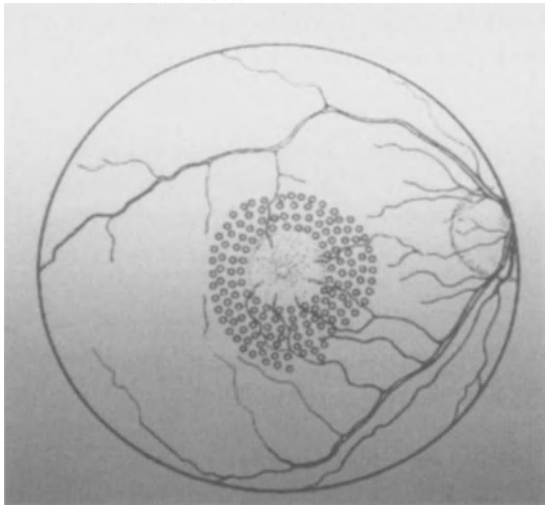

Figure 1. Schematic diagram illustrating the distribution of the macular grid laser burns in the presence of diffuse macular macular edema.

Technique of laser therapy

Today, the focal technique is preferable for all eyes in which it is possible to identify discrete areas of microvascular abnormalities responsible for macular edema. In other cases, when large hard exudates, and/or cystoid macular edema and/or widespread blood-retinal barrier breakdown are present, it is better to perform a grid photocoagulation [5, 8–10]. In the focal technique, 100–200 micrometers spots must be applied with a power able to obtain a moderate retinal whitening. Exposure time must be as long as possible, although sometimes it must be shortened because of the paracentral location of the target sites. By this way it is possible to obliterate the sites of the blood-retinal barrier which give rise to hard exudates and may result in edematous maculopathy. For focal treatment the wavelengths with great affinity for hematic pigments must be preferred. Among these are the yellow dye laser, the monochromatic Argon-green and the double frequency Nd:YAG laser. However, good results can also be achieved by longer wavelengths [11]. In the grid technique 100–200 micrometer non confluent spots producing a grey effect are placed over the edematous area (Figure 1). When grid treatment is bilateral, it is advisable to spare the median raphe in order to avoid paracentral gridlike scotomas. In order to obtain the grey effect, the power employed must be as low as possible. The photocoagulative paramemeters must be modified many times during each session according to the severity of the edema and the

grade of pigmentation. Longer wavelengths, such as krypton red and diode laser, are to be preferred to perform grid laser treatments.

Pathophysiologic mechanisms of photocoagulation

The exact pathophysiologic mechanism of laser pohotocoagulation in grid treatment is still unknown. On the basis of experimental evidence, various mechanisms have been advanced: laser treatment could open new pathways of metabolic exchange between the subretinal space and choriocapillaris by altering the barrier function of the retinal pigment epithelium. However, Wallow [12] has observed that soon after photocoagulation, a passage of tracer material occurs towards the retina and not in the other direction. Whether this effect is time-dependent is not yet known. Marshall [13] found that retinal vessels overlying outer retinal laser lesions showed marked focal endothelial cell division. This finding was more striking with krypton red than with argon green laser. Laser photocoagulation may disrupt the outer blood-retinal barrier with diffusion of metabolites stimulating endothelial repair and recovery of the inner blood-retinal barrier [14]. On the other hand, grid photocoagulation may improve the malfunctioning population of the retinal pigment epithelial cells which are unable to maintain effectively the outer blood-retinal barrier [12]. Finally it is possible that the coagulative necrosis of the pigment epithelium produces a diffusible factor that promotes the restoration of the blood-retinal barrier [14].

In conclusion, grid technique is indicated in cases where macular edema is diffuse and in which it is difficult to identify discrete areas of dye leakage on fluorescein angiograms. Spots must be 100–200 micrometers in size, non confluent, and placed over the whole edematous area. The retina must show a grey effect. Krypton red and idode laser are the most suitable laser wavelengths to employ.

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Grid photocoagulation for focal diabetic macular edema with focal leaks and hard exsudates involving the peri-foveolar area

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Abstract. This study was conducted to determine whether indirect grid laser therapy is effective in reducing focal diabetic macular edema characterised by focal leaks and hard exsudates involving the para-foveal area (less than 300 microns from the center of the fovea). Since focal coagulation of microaneurysms in such a critical location can be deleterious, indirect grid pattern laser treatment may be used in such cases.

Patients and methods

We retrospectively reviewed thirty eyes of twenty-three diabetic patients. 11 patients were female and 12 male. 12 Patients had type I and 11 had type II diabetes mellitus. The patient's age ranged from 25–80 years (mean age 55 years). The known duration of diabetes ranged from 1 to 24 years (mean of 13 years). The glycemic control evaluated by hemoglobin A1c was suitable in 14 patients (HbA1c less than 8%) and poor in 9 patients (HbA1c greater than 8%). Four patients had diastolic blood pressure greater than 95 mmHg, and three patients had hyperlipemia. No patient had renal failure. Exclusion criteria were recent pan-retinal photocoagulation (less than 6 months), significant lens opacities, centro or subfoveal exsudates, macular serous detachment and visual acuity less than 20/200. Ocular evaluation before and after treatment consisted of best corrected visual acuity, stereoscopic biomicroscopy, colour fundus photography, red-free, blue light, red light fundus photography and intravenous fluorescein angiography.

Conventional grid pattern photocoagulation was applied to the thickened retina using Argon-green wavelength (532 nanometers), 100 micron spot size, 0.10 second exposure. The two most important goals were to obtain a *barely visible subthreshold burn*, at the level of the outer retina or the retinal pigment epithelium , and to avoid the 250 microns away from the edge of the foveal avascular zone. The objective was not to produce closure of the microan-

eurysms which is the currently preferred technique for laser treatment of focal diabetic macular edema. The grid photocoagulation was performed in all eyes in one session and by one surgeon (CGA).

Follow-up examinations were performed every 3 months, including best corrected visual acuity and stereoscopic fundus biomicroscopy. Intravenous fluorescein angiography was recommended for deteriorating eyes. A supplemental treatment was applied at 6 months for residual edema in 10 eyes. The review period ranged from 6 to 132 months with a mean follow-up of 71 months.

Results

Anatomical findings

Six to eight months following treatment resolution of retinal thickening and disappearance of microaneurysms appeared in 25 eyes (83%). Eight to ten months after treatment the hard exsudates had disappeared in the same eyes. Five eyes worsened. In 2 eyes macular serous detachment occurred, while 3 eyes developed a centrofoveal exsudate. Out of these worsening eyes three were pseudophakic.

Visual results

All eyes which were reviewed for this study presented a visual loss of two Snellen lines or more. As previously explained, eyes with initial severe macular conditions such as serous detachment, centro-foveolar exsudate and visual acuities less than 20/200 were excluded.

The initial visual acuities were $>$ 20/40 in 10 eyes, equal to 20/40 in 8 eyes and $<$ 20/40 in 12 eyes. Final visual acuities were $>$ 20/40 in 13 eyes, equal to 20/40 in 7 eyes and $<$ 20/40 in 10 eyes. Visual acuity improved in 10 eyes (33%), was unchanged in 13 eyes (43%) and worsened in 7 eyes (23%).

Discussion

The well accepted ETDRS studies have shown in their initial reports that diabetic eyes with clinically significant macular edema involving the center were at a very high risk of losing vision within 12 months. For such eyes, prompt direct photocoagulation of the focal leaks should be considered. However, the proximity of the leaking microaneurysms to the foveal avascular zone has to be taken into account. Since photocoagulating such lesions can induce bothersome side effects such as enlargement of the laser scars and scotomas [1, 2] the ETDRS suggested optional treatment for lesions located less than

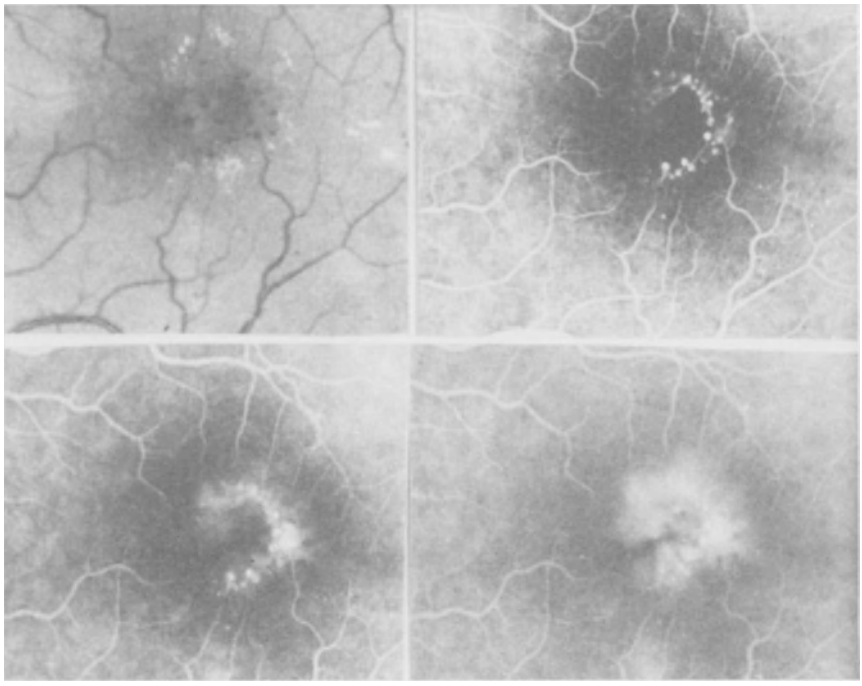

Figure 1. 55-year-old male patient with type I diabetes of 18 years duration which was well controlled (HbA1c 8%). Top left: pretreatment red-free fundus photograph showing foveolar thickening with a few parafoveal exsudates and numerous microaneurysms located along the perifoveolar arcade. Top right: Fluorescein angiogram in the early phase showing microaneurysms surrounding the foveal avascular zone (FAZ). Bottom left and right: Fluorescein angiogram in the mid and late phases. Note the leaking microaneurysms with central cyst formation involving the FAZ.

500 microns from the fovea. In the current study, we included eyes which were characterized by foveal thickening and hard exsudates induced by microaneurysms located closer than 500 microns to the fovea. In our experience, spontaneous improvement is rarely observed and the natural history carries a bad prognosis [3]. Leaving those eyes untreated or creating an untreated control group would not comply with ethical standards. On the other hand, previous laboratory and clinical studies with krypton red or diode laser suggest that much of the beneficial effect of photocoagulation in retinal vascular diseases derives from processes dependent on energy deposition in the retinal pigment epithelium rather than in the retinal vessels themselves. This beneficial effect could be related to biochemical factors released by the coagulated retinal pigment epithelial cells. These factors may diffuse to the inner retina with a stimulatory effect on the vascular endothelium and inducing closure of the microaneurysms and reestablishment of the inner blood-retinal barrier

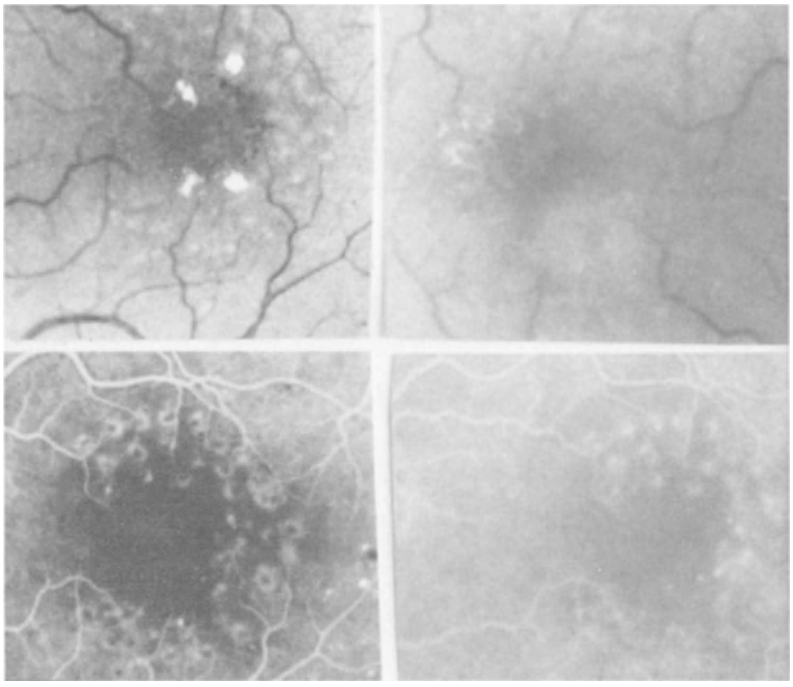

Figure 2. Top left: red-free fundus photograph four months following laser grid treatment which spared the 250 microns around the FAZ (three rows of barely visible burns) showing enlarged hard exsudates without increase of thickening in foveal area. Top right: Red free fundus photograph 16 months after grid treatment showing the disappearance of microaneurysms and hard exsudates. Note the barely visible non enlarged grid scars. Bottom left and right: Fluorescein angiography in the early and late phases showing the disappearace of the microaneurysms and the resolution of the central macular cyst.

[4–7]. For these reasons we proposed ten years ago to perform indirect pattern grid laser therapy using both pure Argon green wavelengths (532 nm) whose absorption by luteal pigment is quite low (less than 10%) and threshold burns which minimize macular damage as demonstrated by central visual fields [3]. The anatomical and functional outcomes of the present study support the beneficial effect of indirect grid photocoagulation in diabetic focal edema involving the centre.

Conclusion

This study suggests that indirect grid laser photocoagulation using Argon green wavelengths is effective in reducing focal diabetic macular edema with disappearance of non coagulated microaneurysms. Since this procedure in-

duced fewer side effects, it could be performed in place of direct focal photocoagulation when microaneurysms are located close to the foveal avascular zone.

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Grid laser treatment of macular edema in macular branch retinal vein occlusion

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Abstract. *Aim*: Macular branch retinal vein occlusion (MBRVO) is a subgroup of branch retinal vein occlusion in which the occlusion is limited to a small venous vessel draining a sector of the macular region. The present study aims to evaluate the efficacy of grid laser treatment for macular edema in MBRVO. *Methods*: 77 Patients with MBRVO of recent onset were prospectively studied during a 24 month period. Eyes were randomly assigned to a grid laser treatment group and to a control group. Clinical parameters such as visual acuity, presence of macular edema and angiographic features were recorded during the follow-up period. *Results*: Visual acuity increased significantly in both groups after 3 months of follow-up ($p<0.001$) and after 1 year of follow-up ($p<0.005$). No additional improvement was noted at the two year control. There was no statistical difference between the two groups. *Conclusions*: The visual prognosis of MBRVO is not improved after grid laser treatment of macular edema. This suggests that sudden ischemic damage to central photoreceptors rather than macular edema is the main factor for permanent visual acuity reduction.

Introduction

Macular branch retinal vein occlusion (MBRVO) is a subgroup of branch retinal vein occlusion in which the occlusion is limited to a small venous vessel draining a sector of the macular region. The functional impairment consequent to MBRVO may be severe, although the ophthalmoscopic changes may be minimal [1, 2], this difference depending on the extent of macular edema or central ischemic changes [3]. The present study aims to evaluate the effectiveness of grid laser treatment on macular edema of patients with MBRVO.

Patients and methods

Inclusion criteria for the study were a recent occurrence of MBRVO (within 15 days), significant macular edema and visual acuity less than 0.6. Significant macular edema was defined as stereoscopically determined retinal

thickening of one optic disc area or larger in size, involving the fovea. Exclusion criteria were media opacities, previous laser treatment, previous surgical therapy or any other associated retinal pathology. Each patient underwent an ophthalmic assessment including stereophotography and fluorescein angiography at the time of the entry into the study, and after 3, 12 and 24 months. Best corrected visual acuity was determined at each visit using a standard Snellen chart. The examiner of visual acuity was unaware whether the patient belonged to the treatment or the control group. Changes of Snellen visual acuity of more than 2 lines were considered significant. The patients were randomly assigned to laser treatment or the control group. The grid laser treatment was performed only after the 3 month visit in order to allow for a sufficient clearing of retinal hemorrhages. We used a krypton laser with 100 micron spots size, power of 100–200 mW and of 0.5 sec duration. The laser treatment was directed at the area of capillary leakage identified by fluorescein angiography avoiding the foveal avascular zone. The assessment of the macular edema was performed by two authors (MBP and SS) comparing the stereophotographs and fluorescein angiographies (late phases of 10 min). The interobserver concordance was 96% and 94% of cases respectively. A third author (GR) was consulted to define uncertain cases. Each patient was informed about the purpose of the study and provided informed consent. Statistical analysis was carried out using the Student's *t*-test and the chi-square test.

Results

Out of 98 patients with MBRVO only 77 patients fulfilled the inclusion criteria (78.5%), since 11 patients had a visual acuity of more than 0.6. Nine patients were lost during the follow up (one patient died one month after the inclusion into the study, and 8 patients refused the 3 month control visist). Thus only 68 patients were considered for the evaluation of this study. The mean age was 69.5±6.8 years, with 41 male and 27 female patients. 33 patients underwent laser treatment, and 35 patients were followed in the control group. The complete results of visual acuity changes are reported in Tables 1, 2.

Baseline visual acuity in the laser treatment group was 0.41±0.6 (range: 0.2–0.6). At the 3 month control visit visual acuity had increased to 0.60± 01.7 (range: 0.3–0.9), at the 12 month visit to 0.68±0.15 and at the 24 month visit to 0.70±0.16. Baseline visual acuity in the control group was 0.39±0.18 (range: 0.2–0.6). At the 3 month visit it had increased to 0.61±0.17 (range: 0.3–0.9), at the 12 month visit to 0.69±0.16 and at the 24 month visit to 0.71±0.16. Statistical analysis showed a significant difference between base-

Table 1. Visual acuity mean values (+/− SD)

	Treated	No Treatment
Baseline	0.41+/−0.16	0.39+/−0.18
3 months	0.60+/−0.17*	0.61+/−0.17*
12 months	0.68+/−0.15**	0.69+/−0.16**
24 months	0.70+/−0.16	0.71+/−0.16

*Statistically significative difference ($p<0.001$).
**Statistically significative difference (<0.05).

Table 2. 2-line change in visual acuity at the 3-month control

	Treatment	No Treatment
Improved	24 (72.7%)	26 (74.2%)
Unchanged	9 (27.2%)	9 (25.7%)

line visual acuity and vision at 3 months ($p<0.001$) and at 12 months ($p<0.05$). Table 2 shows the 2-line change in visual acuity at the 3 month visit. Macular edema had improved at the end of follow-up in 29 treated patients (87.8%) and in 28 non-treated patients (80%) using stereophotographic evaluation. Edema improved in 25 treated patients (75.5%) and in 24 non-treated patients (68.5%) using fluorescein angiograms for the evaluation (see Table 3).

Discussion

MBRVO is a subgroup of branch retinal vein occlusion which may show only subtle clinical and angiographic clues such as collateral vessels or microaneurysms in a limited sector of the macular region [2]. In spite of its discreet appearance, MBRVO can adversely affect visual acuity chiefly due to macular

Table 3. Macular edema

	Improved		Unchanged	
	Treatment	No Treatment	Treatment	No Treatment
Stereophotography	29 (87.8%)	28 (80%)	4 (12.1%)	7 (20%)
Fluorescein angiography	25 (75.5%)	24 (68.5%)	8 (24.2%)	11 (31.4%)

edema and central ischemic changes in the fovea [3]. We decided to perform early grid laser treatment in eyes with MBRVO which had significant macular edema in order to promote a more rapid increase in visual acuity than would be expected given the natural history. However, the present study indicates that the natural evolution of the disease is relatively good, considering that visual acuity spontaneously improved in the control group to the same degree as in the laser treated group. The favorable natural history of eyes presenting ischemic macular edema after branch retinal vein occlusion has already been highlighted by Finkelstein [4] whose analysis also included cases with MBRVO. Although the Branch vein occlusion study has shown a benefit of grid laser treatment in macular edema [5], a retrospective and uncontrolled study had already reported ineffectiveness of grid laser treatment in MBRVO [2]. This difference may be due to the fact that the Branch vein occlusion (BVO) study refers to the occlusion of a major branch of a retinal vein.

We are aware of the fact that our study does not have a high enough number of patients to draw definite conclusions. However, the following points may explain why no further increase in visual acuity was obtained with laser treatment in MBRVO. The Branch vein occlusion study selected cases with occlusion lasting from 3 to 18 months with macular edema that had reduced visual acuity to 20/40 (0.5) or worse. In the present study we treated early occlusions (15 days to 3 months) with a higher maximal baseline visual acuity (up to 0.6). Furthermore, not all eyes with branch vein occlusion show damage along the perifoveal capillary network, whereas all eyes with MBRVO have an enlargement of the foveal avascular zone secondary to the break of the perifoveal capillary arcade which was associated with a drop in vision [3]. It is also well known that those eyes with intact capillary arcades have a significantly better visual prognosis than those with broken arcade [6]. The abrupt changes to the central photoreceptors may be regarded as the main causative factor of the functional impairment after MBRVO and grid laser treatment is therefore not able to reduce macular edema more efficiently than the reduction seen during the natural evolution.

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The place of vitreoretinal surgery in the treatment of macular oedema

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Introduction

Advances in vitreoretinal surgical techniques over the last twenty-five years have expanded the list of indications for vitreoretinal surgical treatment. There are several conditions in which macular oedema is associated with vitreous pathology that is amenable to surgical treatment. This article reviews the role of vitreoretinal surgery in the management of many of these conditions including pseudophakic macular oedema, epiretinal membranes, uveitis, vitreomacular traction syndrome, and diabetic maculopathy.

Irvine–Gass syndrome

It was the observations of Irvine in 1953 which gave the first hint that vitrectomy might have a role in the treatment of macular oedema [1]. He described a syndrome consisting of conjunctival injection, photophobia, reduced vision, and increased flare in eyes which had undergone cataract extraction, complicated by rupture of the anterior hyaloid face. The syndrome appeared two to three months after intracapsular cataract extraction. Irvine observed that cases with persistent visual loss were associated with a vitreous strand to the section.

In 1966 Iliff described what was probably the first application of vitreous surgery in the treatment of macular oedema [2]. He treated cases with 'Vitreous Tug Syndrome', which were similar to those of Irvine. In all patients, the visual acuity was good two months after cataract surgery, but subsequently deteriorated. The surgical technique involved softening the eye, which was achieved using a combination of mannitol, urea, and occasionally a posterior sclerotomy! He then injected air into the anterior chamber, and used a bent needle to hook the strands of vitreous. These were then cut with fine scissors. His surgical results are shown in Table 1, from which

Table 1. Visual results for nine patients of Illif [2] with 'Vitreous-tug Syndrome'

Patient	VA @2/12	Pre-op VA	Final VA
1	20/30	20/100	20/35
2	20/20	20/80	20/30
3	20/30	20/100	20/400
4	20/25	20/70	20/20
5	20/25	20/50	20/25
6	20/25	20/200	20/30
7	20/20	20/70	20/20
8	20/20	20/70	20/30
9	20/25	20/200	20/60

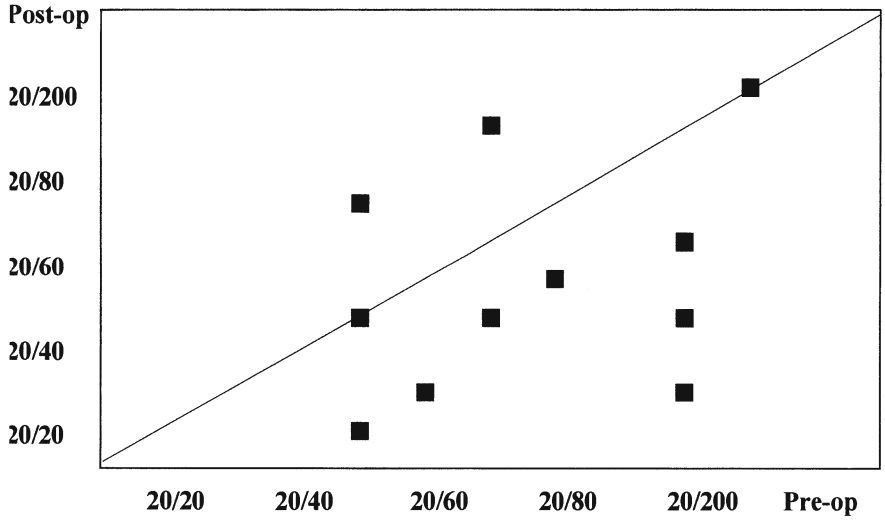

Figure 1. Visual results of anterior vitrectomy in Irvine–Gass syndrome (Fung [4]).

it can be seen that in the majority of patients, the visual acuity improved post-operatively.

The same year, a landmark paper by Gass and Norton established the central role of macular oedema as the cause of visual loss in vitreous-tug syndrome (now known as Irvine–Gass syndrome) [3]. The aetiology of the oedema was poorly understood and theories suggesting a dominant role for vitreous traction, or inflammation both had their advocates. Anti-inflammatory

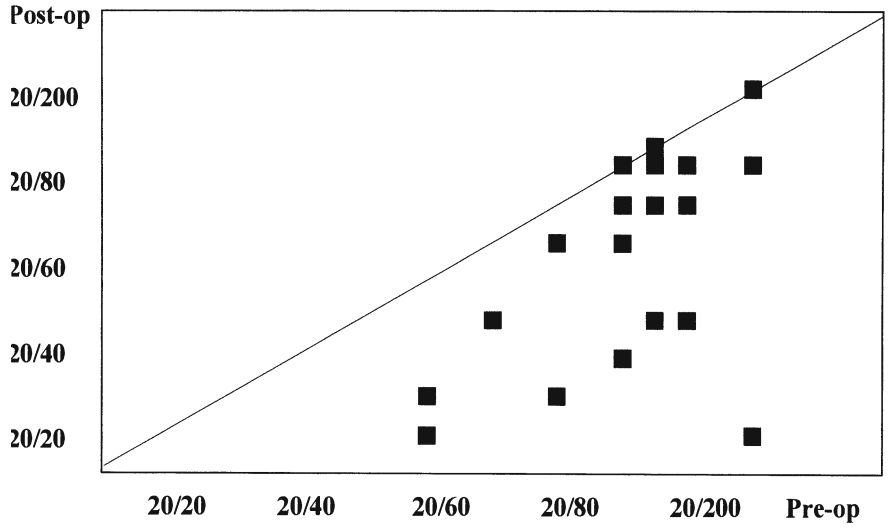

Figure 2. Visual results of pars plana vitrectomy in vitreomacular traction syndrome [16].

treatment was tried with limited effect, but attempts to deal with the vitreous traction directly were more successful. In 1980 Fung published a series of patients treated by anterior vitrectomy using the Kloti stripper via a limbal approach [4]. All patients had angiographically proven cystoid macular oedema (CME) associated with vitreous to the section, following intracapsular cataract extraction, for 6 months or more. The results are shown in Figure 1, and were sufficiently encouraging that a large scale, prospective, multicentre, randomised controlled trial was undertaken [5]. A total of 136 eyes were included from 15 centres in the USA. Sixty-eight eyes were randomised to surgery or control. The rate of improvement (defined as an increase in visual acuity of two or more lines) was 29/43 (67%) in the treatment group, compared with 8/24 (33%) in the control group. This difference was statistically significant ($p<0.01$). In addition there was a very low rate of complications. This study established beyond doubt, the role of vitrectomy in the management of Irvine–Gass syndrome.

Epiretinal membrane

Idiopathic epiretinal membranes are associated with symptoms of distortion and visual loss. Oedema can often be demonstrated using fluorescein angiography, and is thought to contribute to the visual impairment. Machemer was the first to apply the techniques of vitreous microsurgery to epiretinal

Table 2. Visual improvement following vitrectomy in published series of patients with posterior uveitis

Study	Year	Number	Improved
Werry et al. [8]	1987	74	70%
Bovey et al. [9]	1992	30	96%
Dugel et al. [10]	1992	11	64%
Messerli et al. [11]	1992	106	61%
Heiligenhaus et al. [12]	1994	28	82.8%
Verbraeken [13]	1996	25	56%

membranes, and he successfully removed them in a series of 6 patients using a bent needle [6]. The results in these patients are shown in Table 2. Five improved, three of whom maintained their improvement. There have been several large series published since and vitreoretinal surgery is now an established technique in the management of symptomatic epiretinal membranes.

The presence of CMO generally suggests a worse prognosis for visual improvement following surgery. In a large study of prognostic factors, the presence of preoperative CMO was found to have an adverse association with postoperative visual acuity. However, following multivariate regression analysis, it did not add to the accuracy of the model when other factors were taken into account [7]. Fluorescein angiography may be used to quantify the degree of CMO pre-operatively, but there is disagreement in the literature concerning the value of fluorescein angiography in the prediction of visual outcome.

Uveitis-related CMO

MO is a significant cause of visual loss in patients with chronic posterior uveitis. There are many indications for vitrectomy in such cases, including biopsy for diagnosis, media opacity, and epiretinal membranes. Most studies have reported visual improvement following surgery (Table 3) [8–13]. The majority of these studies also reported a beneficial effect on CMO.

Supportive evidence for the role of vitrectomy in the treatment of uveitis related CMO comes form a study of 116 eyes with peripheral uveitis followed up for a mean of 5 years [14]. The vitreous was found to be attached in 78% of eyes with CMO, but in only 22% of eyes without CMO (p=0.01). A similar difference was found for visual loss (57% v 21%). However, the indications for vitrectomy in uveitis, in the absence of media opacity and the need for

diagnosis, need further clarification. In particular a randomised, controlled trial is necessary to determine whether CMO is an indication in the absence of other factors.

Contraction of posterior hyaloid

Vitreomacular traction syndrome

A syndrome consisting of partial separation of the posterior hyaloid, with continuing traction over the posterior pole has been described recently. The condition is associated with visual loss and CMO. It was first described by Jaffe in 1967 [15], but recent interest has been stimulated by the application of vitreous surgery in its treatment. Surgical removal of the remaining posterior hyaloid has been shown to be effective in resolving the CMO with subsequent improvement in vision. In a series of 20 patients with the syndrome, 19/20 (95%) had CMO clinically preoperatively, and 16/20 (80%) had leakage on fluorescein angiography. Following vitrectomy, the CMO completely resolved in all but 3 cases (15%) [16].

Diabetic maculopathy

CMO can also occur in association with posterior hyaloidal traction in some cases of diabetic macular oedema. These cases are characterised by a taut and thickened posterior hyaloid, and diffuse leakage at the macula on fluorescein angiography. It has been shown recently that vitrectomy can improve the visual acuity of some patients with this condition. In a series of ten patients who underwent vitrectomy, the macular oedema and traction completely resolved in 8 (80%), and partially resolved in 2 (20%) [17]. The visual acuity improved by two or more Snellen lines in 7 (70%). The factors producing macular oedema in diabetics are multiple, but it is possible that the posterior hyaloid may play a role, at least in some cases. Supporting evidence comes from the observation that diabetic eyes with macular oedema have a lower prevalence of separation of posterior hyaloid.

Conclusion

It is clear that pathology of the vitreous body is associated with macular oedema in several different conditions, although details of the pathophysiology remain to be determined. Vitreoretinal surgical techniques can be effective in the management of macular oedema in the majority of these conditions.

However, more precise indications for vitrectomy, particulary in uveitis, need to be defined by further clinical trials.

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Vitrectomy for traction macular edema

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Abstract. *Purpose*: Traction macular edema may develop through contraction of macular epiretinal membranes (ERM), or due to persistant vitreomacular traction during the evolution of vitreomacular traction syndrome (VMS). The purpose of this retrospective study was to determine the effect of vitreous surgery and the release of the vitreomacular traction or the removal of epiretinal membranes, on the evolution of traction induced macular edema. *Material and methods*: Fourteen eyes from 14 patients presenting with idiopathic or secondary epiretinal membranes, and 11 eyes from 10 patients presenting with vitreomacular traction syndrome, underwent vitrectomy for reduced vision and cystoid macular edema, identified by slit-lamp examination and fluorescein angiography. No coexistent ocular conditions that might have caused macular traction were present. History, preoperative eye examination, operative findings, postoperative course and final examination as well as pre- and postoperative fluorescein angiography were reviewed. *Results*: In the ERM group, cystoid macular edema disappeared in all cases during the postoperative period and the mean visual acuity (VA) at the end of the follow-up (0.48 ± 0.23) significantly increased compared to the preoperative one (0.29 ± 0.2) (p=0.004). In the group of patients suffering from VMS, the posterior vitreous traction on the macula was released and macular edema disappeared in all cases but one. The mean v.a. at the end of the follow-up (0.42 ± 0.24) significantly increased compared to the preoperative one (0.18 ± 0.1) (p=0.01). Complications included intraoperative small petechias and postoperative progressive nuclear sclerosis, retinal detachment and retinal pigment epitheliopathy. *Conclusions*: Cystoid macular edema may develop secondary to vitreomacular traction syndrome or epiretinal membrane contraction. Vitrectomy is effective in releasing macular traction which, in turn, may induce a decrease of the macular edema with improvement of visual acuity.

Introduction

Vitreous traction on the macula has been implicated in the pathophysiology of numerous ocular conditions, including aphakic cystoid macular edema, tractional retinal detachment of the posterior pole, retinal detachment associated with macular hole, and idiopathic macular holes [1]. Age related posterior vitreous detachment may be incomplete posterior to the equator, which may result in persistent vitreous traction on the posterior retina, referred to as vitreomacular traction syndrome (VMS). Macular traction is frequently accompanied by cystoid changes in the neurosensory retina of the macula, causing chronic macular edema and inducing metamorphopsia, photopsia, micropsia and decreased visual acuity [2].

Similar clinical and functional findings result due to contraction of epiretinal macular membranes (ERM) either idiopathic, or secondary to numerous clinical conditions, including ocular inflammatory disorders, vasoproliferative retinal ischemic microangiopathies, intraocular tumors, ocular trauma, post retinal detachment repair, after photocoagulation or cryotherapy [3–5]. The severity of symptoms experienced will depend on the membrane thickness, the degree of retinal distortion, the degree of macular edema and the development of full thickness retinal folds [4–6].

Although the epiretinal macular membranes and the vitreomacular traction syndrome are distinct clinical conditions, the ultrastructural features of epiretinal macular tissue from eyes with those conditions are similar. They are expressing fibrous astrocytes, fibroblasts and myofibroblasts [7], suggesting common features in pathogenesis.

In the long term evolution of vitreomacular traction syndrome and macular epiretinal membranes contraction, further development of cystoid macular changes induces an additional decrease in visual acuity [8]. Exceptionally spontaneous complete vitreomacular separation allows resolution of cystoid changes and improvement in visual acuity [8].

The purpose of this study was to determine the effect of vitreous surgery and release of the vitreomacular traction or the removal of epiretinal membranes, on the evolution of traction induced macular edema in eyes with ERM and VMS.

Material and methods

We performed a retrospective study on 14 eyes (14 patients) presenting ERM and 11 eyes (10 patients) presenting VMS. All eyes suffered from traction macular edema and presented reduced vision. All the above cases had been operated from 1994 to 1997 at the University Eye Clinic of Geneva. Only eyes with nonvascular-appearing ERM, both idiopathic or secondary, confined to the macula were included. No coexistent ocular conditions that might have caused macular traction were present. All the eyes operated on were symptomatic and presented with clinically and angiographically confirmed macular edema. Mean duration of follow-up was 20.5 months, with a minimum of 12 and a maximum of 36 months for the group presenting ERM, and 16 months, with a minimum of 12 and a maximum of 33 months for the group presenting VMS.

Conventional vitreous surgery was conducted with a three-port system which included a separate infusion cannula, a port for fiberoptic light probe and a port for use of a vitrectomy probe, or an intraocular forceps. The central vitreous gel was removed first, then the posterior vitreous interface surround-

ing the posterior pole was cut to relieve anteroposterior vitreous traction on the macula and the optic nerve head.

In cases with epiretinal macular membranes the posterior cortical vitreous was in all cases separated from the retinal surface. The edge of the epiretinal membrane was engaged with a Flynn cannula and gently elevated while the cannula was moved tangentially along the inner retinal surface. After delimitation, the membrane was grasped with a diamond-coated end-opening forceps and peeling was completed. The membrane was usually removed as a single piece. Occasionally it had to be cut at a point of firm adhesion to the retinal surface. Sometimes the membrane was found to be constituted of multiple layers.

Information was recorded based on the history, preoperative eye examination, operative findings and postoperative course. Items recorded from the patient's history included age, sex, complaints of decreased vision or metamorphopsia. Preoperative and postoperative examination included: VA, grade of lens opacity, aphakia or pseudophakia, posterior vitreous detachment, retinal striae, retinal dragging, retinal vascular distortion, macular thickening and cystoid macular edema. Preoperative and postoperative fluorescein angiographic findings, particularly retinal vascular leakage and cystoid macular edema were also reviewed.

Statistical analysis was performed using the paired Student-*t*-test. A $p < 0.05$ was considered as significant.

Results

Preoperative findings

In the ERM group the mean age of the patients was found to be 70 years with a range of 60 to 86 years. Seven (50%) were men and 7 (50%) were women. There were 6 (43%) right eyes and 8 (57%) left eyes. Four (28.5%) eyes were pseudophakic. The mean preoperative VA was 0.29 ± 0.2.

In the SVM group the mean age of the patients was found to be 72 years with a range of 53 to 84 years. Six (54.5%) were men and 5 (45.5%) were women. There was 5 (45.5%) right eyes and 6 (54.5%) left eyes. Six (54.5%) eyes were pseudophakic. The mean preoperative VA was 0.18 ± 0.11.

All eyes presented cystoid macular edema confirmed by biomicroscopy and fluorescein angiography.

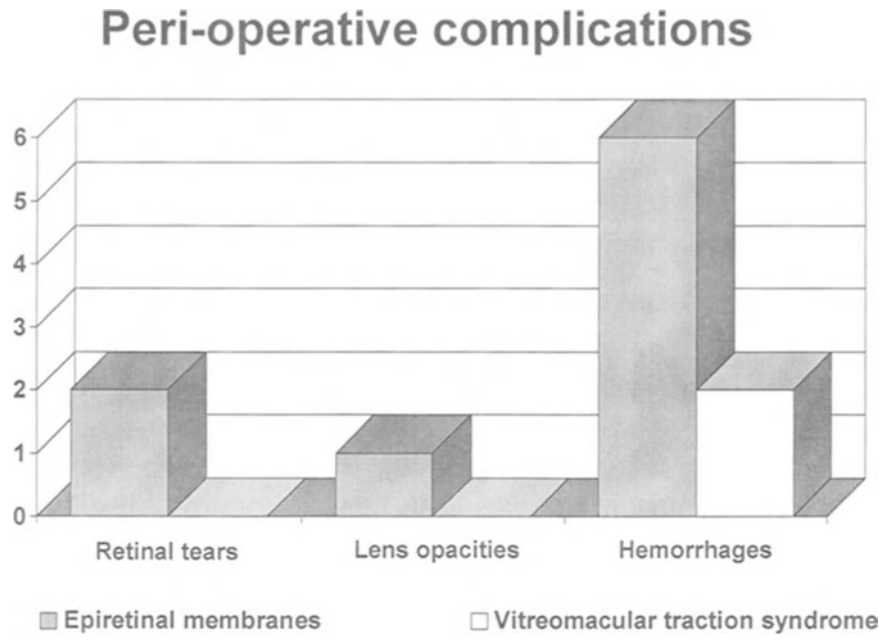

Figure 1. Schematic diagram showing the rate of peri-operative complications of epiretinal membranes (ERM) and vitreomacular traction syndrome (VMS) surgery.

Perioperative complications

Intraoperatively, small petechias, from the perifoveal capillary bed were reported in 6 cases, presenting ERM, and in 2 cases, presenting VMS. None involved the fovea or caused a decrease in postoperative VA. Peripheral retinal tears were observed in 2 cases, presenting ERM, and none of the cases, presenting VMS. These were treated intraoperatively by a peripheral vitrectomy and transscleral cryoapplication. No secondary peripheral tears or retinal detachment were observed in those eyes. In one eye with ERM, intraoperative significant nuclear opacification of the crystalline lens was observed. Although it had not impaired the completion of the operation it was followed by rapid post operative progressive nuclear opacification, requiring phakoemulsification after three months (Figure 1).

Postoperative complications

Accelerated nuclear sclerosis of the crystalline lens was the most common postoperative complication encountered. It was observed in 6 of 10 phakic eyes in the ERM group and in 3 of 5 phakic eyes in the VMS group, within 12 months after vitrectomy for traction macular edema. No similar progression

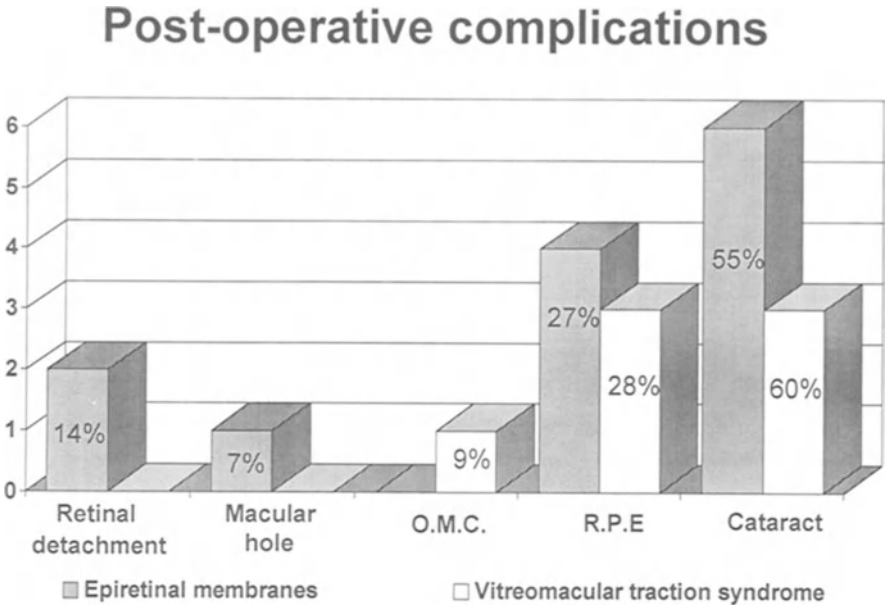

Figure 2. Schematic diagram showing the rate of post-operative complications of epiretinal membranes (ERM) and vitreomacular traction syndrome (VMS) surgery.

in nuclear sclerosis was detected in the fellow-eye (Figure 2). Cataract was successfully operated in all cases. Final VA was not significatively different from the mean after cataract ablation in the two groups ($p>0.05$).

Retinal detachment (RD), secondary to a peripheral retinal tear, was observed in 2 (14%) eyes in the ERM group. RD were associated with peripheral retinal tears, and were limited to the periphery, not involving the macular area. Both cases were successfully treated by release of peripheral vitreous traction from the tears to the vitrectomy entrance hole, laser endophotocoagulation and gas injection (SF_6 20%) (Figure 2). None of the VMS eyes developed RD during the post operative observation period.

Marked retinal pigment epithelium abnormalities in the macular area were observed in 4 (28.5%) of the eyes, presenting ERM, and in 3 (27%) of the eyes, presenting VMS, at the final visit. The mean final VA of those eyes was not significatively different from the mean in both ERM and VMS groups ($p>0.05$) (Figure 2).

At the posterior pole a macular hole was observed postoperatively in one case of ERM. It was successfully closed by additional vitrectomy and gas injection (C_3F_8 16%). In that case final VA (0.2) decreased compared to the preoperative one (0.3).

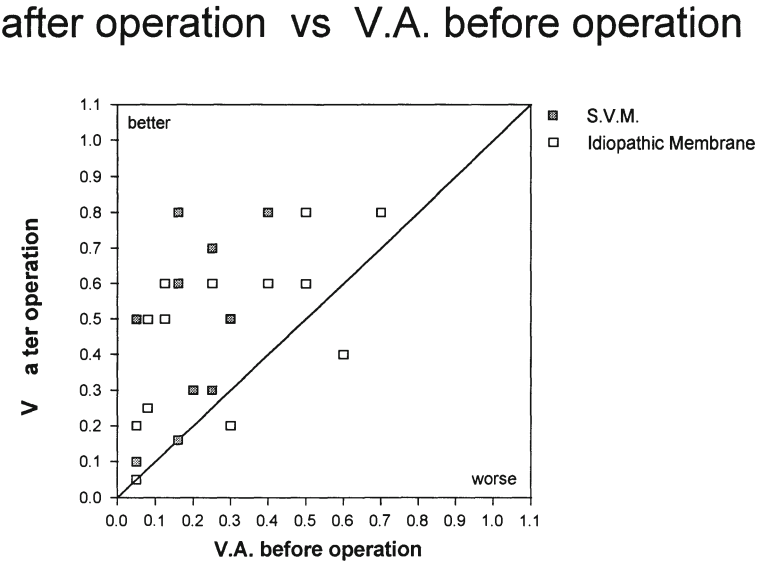

Figure 3. Scattergram showing the postoperative visual acuity (VA) as a function of preoperative VA. Note the global trend to improvement in VA in both MEM and VMS.

Final results

Cystoid macular edema disappeared in all cases, 6 months after vitrectomy, in the ERM group. It persisted in one eye in the VMS group, confirmed both by slit-lamp examination and fluorescein angiography, during the postoperative period. In that case final VA (0.2) decreased compared to the preoperative one (0.3).

The mean VA at the end of the follow-up significantly increased compared to the preoperative one, in both groups (mean preoperative VA: 0.29 ± 0.2, versus mean final VA 0.48 ± 0.23, (p=0.004) in the ERM group, and mean preoperative VA 0.18 ± 0.11, versus mean final VA 0.42 ± 0.24, (p=0.01) in the VMS group). In the ERM group 6 (43%) of the eyes showed at least 4 lines of VA improvement, 3 (21%) of them showed 2 or 3 lines of v.a. improvement, and 2 (14.4%) eyes showed 1 line of VA improvement. One (7.2%) eye maintained his preoperative level in VA and 2 (14.4%) suffered a loss of at least 1 line in VA (Figure 3). In the VMS group, 5 (45.5%) of the eyes showed at least 4 lines of VA improvement, one (9%) of them showed 3 lines of VA improvement, and 2 (18.2%) eyes showed 1 line of VA improvement. Two (18.2%) eyes maintained their preoperative level in VA and one (9%) suffered a loss of 1 line in VA (Figure 3).

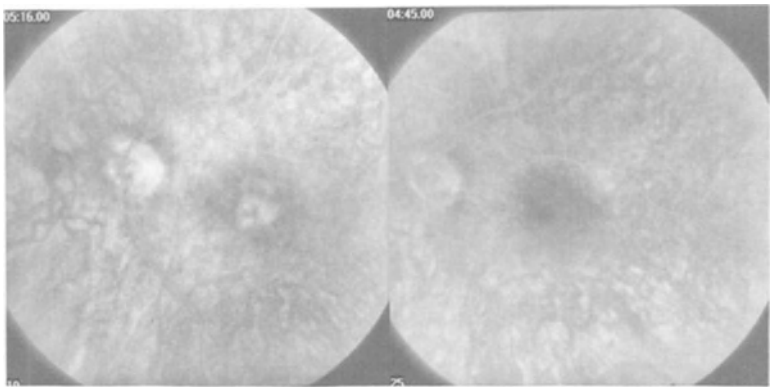

Figure 4. A: Preoperative late phase angiography of an idiopathic epiretinal membrane showing fluorescein leakage and typical appearance of cystoid macular edema. B: Postoperative late phase angiography showing disappearance of the wrinkling and resolution of the macular edema.

Discussion

Traction induced macular edema may develop by contraction of macular epiretinal membranes (ERM), either idiopathic, or secondary to numerous clinical conditions [3, 4]. Previous studies have shown significant visual improvement in 75 to 85% of the eyes operated by vitrectomy for removal of ERM [4, 5, 9]. In addition to visual acuity changes, metamorphopsia was often reduced postoperatively [4, 5, 9]. Several authors suggested that the presence of chronic cystoid macular edema is a poor prognostic factor [10]. Other reports suggested that the presence of macular edema preoperatively did not significantly affect postoperative VA [6, 11]. In our series, peeling of the ERM resulted in regression of traction macular edema in all cases, and was associated to an improvement of at least one line of v.a. in 78.5% of the cases with disappearance of metamorphopsia.

Vitreomacular traction syndrome develops secondary to an atypical process of posterior vitreous separation with persistent macular attachment. This process may result in retinal distortion, retinal blood vessel avulsion and rupture, retinal hole formation and traction retinal detachment [1, 2, 12]. In our series cystoid degeneration of the macula was a prominent preoperative feature in all eyes. A previous clinicopathologic report has demonstrated that such cystic changes are probably caused by prolonged vitreous traction [2]. Vitreous surgery to release the vitreomacular traction resulted in regression of traction macular edema in all cases but one, and was associated with an improvement of at least one line of VA in 73% of the cases in our series.

Postoperative accelerated nuclear sclerosis of the lens is the most common complication encountered after vitrectomy for ERM and VMS. In both groups severe nuclear sclerosis, impairing VA, occurred in 60% of the cases within one year after vitrectomy. After its ablation, no difference in the final visual outcome was found for the group of eyes that did not develop cataract postoperatively. To explain the high rate of accelerated nuclear sclerosis, many hypothesis have been formulated, including operating time, distance of infusion port from the lens, type of irrigating fluid, disruption of the anterior vitreous in the retrolental area, change in intraocular temperature and prolonged exposure to high glucose [13].

Retinal pigment epithelium alterations was the second most common postoperative complication, found in 4 (28.5%) of the eyes, presenting ERM, and in 3 (27%) of the eyes, presenting VMS, at the final visit. The mean final VA of those eyes was not significatively different from the mean in the two group. Although the etiology of these changes remains unclear, many hypothesis have been advanced. RPE changes could be secondary to direct mechanical trauma to RPE and photoreceptors during epiretinal membrane peeling. A phototoxic mechanism, similar to microscope-related phototoxicity, has also been advocated [14, 15].

Peripheral retinal breaks were detected intraoperatively in 2 out of 14 eyes with ERM, a rate similar to what previously reported [10, 11, 13]. Postoperative peripheral retinal breaks, associated to RD, were detected in 2 (14%) of the cases, a rate relatively higher than previously reported [9–11, 13]. As RD occurred within one month after vitrectomy, this suggests that peroperative undetected damage to the retina was probably the cause. In contrast none of the eyes with VMS developed a retinal detachment, presumably to preoperatively observed complete peripheral posterior vitreous detachment. Intraoperative retinal breaks could be managed with cryoapplication in all cases, postoperative ones needed reoperation with vitrectomy to relieve the vitreous traction, laser endophotocoagulation and gas injection (SF_6 20%). In the ERM group eyes, having suffered from postoperative RD, final VA was not statistically different, than in eyes with no postoperative RD ($p>0.05$).

Retinal breaks near the macula have been reported to occur in less than 1% of the cases of ERM after vitrectomy [10, 11]. We observed a postoperative macular hole in one case of the ERM group. It was an eye which had previously suffered from major cystoid macular edema for more than one year.

In conclusion, vitrectomy may be effective in improving cystoid macular edema occurring in eyes with ERM contraction and VMS thus improving visual acuity. Complications related to vitrectomy are relatively frequent and include accelerated postoperative nuclear sclerosis, retinal breaks and RD,

macular RPE modifications and, occasionally, the formation of a macular hole.

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Vitrectomy for macular pucker and vitreomacular traction syndrome

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Abstract. During the course of a so-called posterior vitreous detachment, a thin layer of the posterior vitreous cortex often remains adherent to the underlying retina. Tangential stretch of this vitreous pseudomembrane may cause vitreomacular traction syndrome, edema, and macular hole formation. The same process appears to underlie the development of true epimacular membranes (idiopathic macular pucker). Vitrectomy is generally agreed to be the most appropriate treatment for these clinical situations. We evaluated the incidence of vitreomacular adhesion and of visual improvement after vitrectomy of eyes with macular pucker (group 1; n=60) and vitreomacular traction syndrome (group 2; n=50). Vitreomacular attachment was assessed during vitrectomy under the condition of continuous air infusion. In the two groups, complete or partial vitreous attachment to the macula was observed in 57.4% and 74%, respectively. We conclude that vitreomacular adhesion is a common feature of the two clinical situations. Visual improvement was achieved in 73% of both groups. High rates of postoperative visual acuities of 20/50 or better (60.6% in group-1; 65.7% in group-2 cases) occurred only in eyes with preoperative values of 20/100 or better. It is reported that the visual outcome of vitreoretinal surgery for the two clinical conditions deteriorates with increasing duration after initial manifestation. Vitrectomy should not be postponed in patients who complain of disturbing visual symptoms such as reduced visual acuity, metamorphopsia and disturbance of binocular reading.

Key words: idiopathic epimacular membrane, macular edema, macular pucker, macular traction, vitrectomy, vitreomacular traction syndrome

Introduction

During the course of vitreous collapse and liquefaction, a thin layer of the posterior vitreous cortex often remains adherent to the underlying retina. Tangential stretch of this residual pseudomembrane may lead to macular traction and edema, and, ultimately, to the development of a macular hole. Vitreomacular traction is implicated also in the formation of true epimacular membranes (macular pucker) [1]. Typical symptoms of these three conditions (macular pucker, vitreomacular traction syndrome and macular hole) include a deterioration in visual acuity and metamorphopsia. Many patients also complain of disturbed binocular vision, this being attributable to image

distortion in the affected eye. Visual improvement has been reported after the performance of vitrectomy to relieve vitreomacular traction [2–8].

We compared the functional consequences of vitrectomy in eyes with macular pucker (idiopathic epimacular membranes) and in those with vitreomacular traction syndrome (no evidence of a true epimacular membrane formation).

Methods

We retrospectively evaluated the records of 110 patients who were consecutively operated on by one single surgeon (FK) for two distinct vitreoretinal disorders, namely, idiopathic macular pucker (group 1: 60 eyes between 1983 and 1998) and vitreomacular traction syndrome (group 2: 50 eyes between 1992 and 1998). All eyes in group 1 manifested idiopathic epimacular membranes. Eyes which had been previously treated for retinal breaks, retinal detachment, retinovascular diseases, trauma or uveitis were excluded from the evaluation. In both group-1 and group-2 patients, vitrectomy was indicated due to a substantial deterioration in visual acuity and the manifestation of symptoms such as metamorphopsia or a disturbance in binocular reading capacity.

The age of group-1 patients ranged from 14 to 82 years (median: 70.2 years); that of individuals in group 2 from 8 to 89.8 years (median: 70.9 years). Fifty-eight percent of patients in the former category were female as against 32% in the latter (p <0.01). Prior to surgery, the posterior vitreoretinal situation was assessed by slitlamp biomicroscopy using a three-mirror Goldmann contact lens. During vitrectomy, it was further evaluated under the condition of continuous air infusion. The posterior vitreous was defined as being either completely attached, partially attached with vitreomacular adhesion or completely detached.

Epimacular membranes or vitreous cortex were peeled under microscopic control. The absence or presence of an epimacular layer of vitreous cortex was revealed after gentle suction with a flute needle under conditions of continuous air infusion. In instances where a residual vitreous cortex was thus identified, attempts were made to aspirate and excise it. But in some group-2 individuals, premacular adhesion was so strong as to render impossible the complete removal of this layer.

Visual acuity was measured using a standardized visual acuity projector. Postoperatively, this was determined by unmasked ophthalmologists; not by the surgeon. The follow-up period for group-1 patients varied from 0.2 to 112 months (median: 13.8 months; mean: 24.7±27.3 months); that for individuals

Table 1. Posterior vitreous attachment associated with macular pucker and vitreomacular traction syndrome

Posterior vitreous	Group 1* Macular pucker	Group 2* Vitreomacular traction syndrome
Completely attached	28 (46.7%)	35 (70.0%)
Partially attached	7 (10.7%)	2 (4.0%)
Detached	18 (30.5%)	9 (18.0%)
Not defined	7 (10.7%)	3 (6.0%)
Total	60	50

*Differences between groups were not significant (chi square statistics).

in group 2 from 0.2 to 43.3 months (median: 7.2 months; mean: 9.9±10.2 months).

Postoperative complications, such as retinal detachment, recurrent epimacular fibrosis, macular edema and posterior and/or nuclear cataracts were evaluated in each group.

Statistical analyses included Student's paired *t*-test (comparison of pre- and postoperative visual acuities) and the chi-square test (with Yates' correction for frequencies below 10).

Results

Vitreoretinal situation

The definitive state of vitreoretinal attachment/detachment was usually assessed during vitrectomy. In many cases, large, fluid-filled pockets were observed between the residual posterior vitreous cortex and the vitreous gel. Preoperative examination by slitlamp biomicroscopy had frequently misinterpreted this situation as complete detachment of the posterior vitreous. The state of vitreomacular relation could not be determined unequivocally in 7 group-1 individuals and in 3 of those in group 2.

The posterior vitreous was completely detached in 30.5% of group-1 eyes and 18% of those in group 2. Partial or no posterior vitreous detachment, with vitreomacular adhesion, occurred in 57% and 74% of group-1 and group-2 individuals, respectively, the difference being statistically insignificant (Table 1).

In five group-1 eyes, epimacular membranes could not be peeled away in their entirety; in three of these there was complete, and in one questionable,

Table 2. Visual acuity prior to and at least one month after vitrectomy

Visual acuity (VA)	Group 1* Macular pucker	Group 2* Vitreomacular traction syndrome
No. of eyes	52	46
Initial VA	0.26±0.18	0.29±0.20
Best postoperative VA	0.47±0.29	0.51±0.31
Final postoperative VA	0.37±0.28	0.47±0.33

Values represent means±standard deviations.
*Differences between groups were not statistically significant.

Table 3. Number of eyes (percentages in parentheses) with postoperative visual acuities of 20/50 or better subdivided according to the preoperative value after a follow-up of at least one month

	Group 1 Macular Pucker		Group 2 Vitreomacular Traction	
	Total no. of eyes	Final VA ≥20/50	Total no. of eyes	Final VA ≥20/50
All cases	52	22 (42.3%)	46	28 (60.9%)
Preop VA <20/100	19	2 (10.5%)	11	4 (45.5%)
Preop VA ≥20/100	33	20 (60.6%)*	35	23 (65.7%)**

*p <0.005.
**not significant (chi square statistics; Yates' correction).

vitreomacular attachment. A marginal improvement in postoperative visual acuity was achieved in only one of these five individuals.

Visual acuity

In both group 1 and group 2, initial postoperative visual acuity was improved in 73% of eyes (Figures 1a and 2a), the final value being better than the preoperative one in 57% and 60% of group-1 and group-2 patients, respectively (Figures 1b and 2b). After a follow-up period of 1 month or more, the number of cases with a visual acuity of 20/40 or better increased from 17% preoperatively to 33% postoperatively in group 1, and from 18% to 49% in group 2 (no statistical significance between groups). Means and standard deviations of preoperative, and best and final, postoperative visual acuities in patients with a follow-up time of 1 month or more are presented in Table 2.

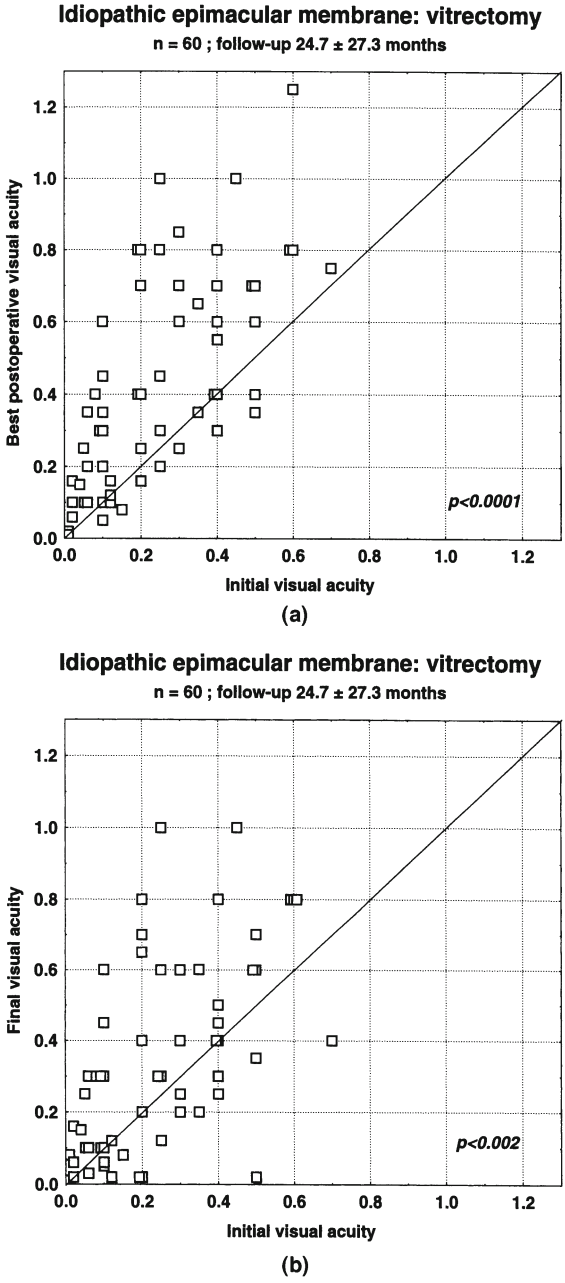

Figure 1. (a) Pre- and best postoperative visual acuity of 60 eyes with idiopathic epimacular membranes (macular pucker; group 1). Follow-up period: 24.7±27.3 months. (b) Pre- and final postoperative visual acuity of 60 eyes with idiopathic epimacular membranes (macular pucker; group 1). Follow-up period: 24.7±27.3 months.

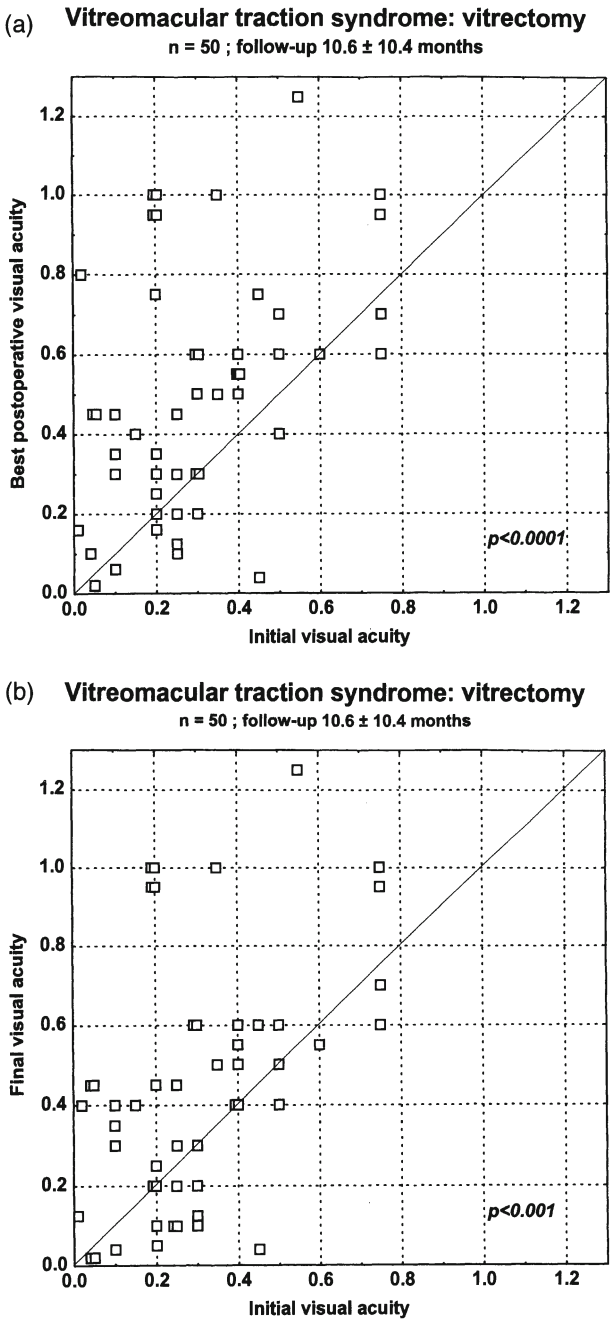

Figure 2. (a) Pre- and best postoperative visual acuity of 50 eyes with vitreomacular traction syndrome (group 2). Follow-up period: 10.6±10.4 months. (b) Pre- and final postoperative visual acuity of 50 eyes with vitreomacular traction syndrome (group 2). Follow-up period: 10.6±10.4 months.

Table 4. Causes of vitrectomy failures (final visual acuity worse than preoperative visual acuity). Follow-up at least one month

	Group 1 Macular pucker	Group 2 Vitreomacular traction syndrome
No. of eyes	16/52	13/45
Cataract	8 (50.0%)	7 (53.8%)
Macular pathology	7 (43.8%)	4 (30.8%)
Residual or recurrent PVR	5 (31.3%)	2 (15.4%)
Keratopathy	0 (0.0%)	1 (7.7%)
Optic atrophy	0 (0.0%)	1 (7.7%)

In order to evaluate the influence of preoperative visual acuity on the final visual outcome, we compared the latter with the former in eyes with initial visual acuities of less than 20/100 and in those with initial values of 20/100 or better. In group 1, a significant visual improvement to 20/50 or better was achieved in 60.6% of individuals with a preoperative visual acuity of 20/100 or better but only in 10.5% of those with preoperative visual acuities of less than 20/100 ($p < 0.005$). The respective rates in group-2 patients were 65.7% and 40%, the difference not being statistically significant (Table 3).

Failures of vitrectomy

A postoperative visual deterioration was defined as failure (Table 4).

Nuclear and/or posterior cataracts developed postoperatively in 23 (38%) and 22 (44%) of eyes in groups 1 and 2, respectively. Group-1 individuals thus affected were between 60 and 80 years of age. In group 2, 19 of the 22 cases were between 50 and 90 years of age; the other 3 fell within the 40- to 50-year range.

Amongst patients with a follow-up period of 1 month or more (52 in group 1 [1.4 to 112 months]; 45 in group 2 [1 to 44 months]), final visual acuity was less than the preoperative value in 16 (31%) group-1 eyes and in 13 (29%) of those in group 2. Within this category, a transient visual improvement was obtained in 7 of the 16 group-1 cases and in 3 of the 13 group-2 eyes. Nuclear and/or posterior cataract formation was the main cause of visual deterioration, macular pathology (edema, cellophane appearance) and residual or recurrent posterior PVR being the next most common (Table 4). Postoperative ret-

inal detachment was never observed. No statistically significant differences between groups existed for any of the various complications manifested.

Discussion

The influence of vitrectomy on visual acuity was evaluated in 60 eyes with macular pucker (group 1) and in 50 with vitreomacular traction syndrome (group 2).

Prior to surgery, complete or partial vitreomacular attachment was apparent in 57% of individuals within the former category and in 74% of those within the latter. Complete detachment of the posterior vitreous (PVD) had occurred in only 30% of the macular-pucker cases and in 18% of those with vitreomacular traction syndrome. In several instances, the posterior vitreous was so firmly attached that the epimacular membrane could not completely be removed. Hirokawa et al. [9] report a 34%-incidence of vitreomacular attachment or traction amongst 250 eyes with biomicroscopically identified idiopathic macular pucker. This observation, as well as our own, contrasts with the findings of Smiddy et al. [1] who reported the pre-existence of posterior vitreous detachment in all 101 vitrectomized eyes with macular pucker. The latter authors thus considered macular pucker (with complete posterior vitreous detachment) to be an anatomic feature quite distinct from vitreomacular traction syndrome (without posterior vitreous detachment).

It should be borne in mind, however, that the majority of surgeons perform vitrectomy whilst infusing the eye with balanced salt solution. Under these conditions, a thin residual epiretinal layer of vitreous cortex may not be revealed. Indeed, we were generally able to identify such a layer only by means of gentle aspiration with a flute needle under conditions of continuous air infusion. It sometimes proved to be impossible to remove this layer completely without running the risk of causing retinal breaks by forced traction. This was found to be the case principally in eyes with vitreomacular traction syndrome.

We conclude that vitreoretinal adhesion and traction are features common to both macular pucker and vitreomacular traction syndrome. However, the pathogenetic mechanisms underlying the progression of vitreoretinal adhesion/traction to the formation of true idiopathic epimacular membranes are as yet unknown.

In both these clinical situations, the aim of vitreoretinal surgery is to relieve vitreomacular traction by peeling away epimacular membranes in pucker cases and by removing the vitreous cortex in eyes with vitreomacular traction syndrome. In our study, there were no differences in pre- and postoperative visual acuities between individuals with either macular pucker or vitreo-

macular traction syndrome. A visual improvement was achieved in 73% of both groups. However, good postoperative visual acuities of 20/50 or better were observed only in eyes with preoperative acuities of 20/100 or better (61% of group-1 and 66% of group-2 cases). These findings confirm those of Gaudric et al. [4] who reported that significantly poorer visual results were achieved with preoperative visual acuties of 20/200 or worse than in ones above 20/200.

A well-known side effect of vitrectomy in these clinical situations is its precipitation of nuclear and/or posterior cataract in 16 to 83% of cases [2, 3, 5–8]. We observed progressive cataracts in 38% and 44% of group-1 and group-2 individuals, respectively. Macular changes were the second most frequent cause of visual loss in both study groups.

Spontaneous resolution of macular pucker and vitreomacular traction syndrome is extremely rare. During a 5-year follow-up of individuals with vitreomacular traction syndrome, cystoid macular edema and a deterioration in visual acuity occurred in 67% of the 53 cases evaluated by Hikichi et al. [10]; the incidence of those with 20/40 vision dropped from 36% (preoperatively) to 8% at the final check up.

In conclusion, vitrectomy improves visual acuity in at least 70% of individuals with macular pucker or vitreomacular traction syndrome, values of 20/50 or better being achieved in one to two thirds of the cases [1, 4, 6, 8, own study]. However, the visual outcome of vitreoretinal surgery for the two pathological conditions deteriorates with increasing time after the initial manifestation of visual symptoms. For this reason, we tend not to postpone vitrectomy in patients who complain of disturbing symptoms.

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Cystotomy for diabetic cystoid macular edema

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Abstract. The purpose of this study was to evaluate the role of vitrectomy with cystotomy in the treatment of diabetic cystoid macular edema (CME). Among 22 eyes of 21 patients with diabetic CME underwent phacoemulsification, intraocular lens implantation, pars plana vitrectomy, induction of posterior vitreous detachment, and cystotomy or cystectomy. Follow-up ranged from 3 to 29 months. Under biomicroscopic examination, Cystoid macular edema was eliminated in 16 of 22 eyes during the follow-up period. Ring-shaped residual edema was observed in one eye. Corrected visual acuity improved in 7 of 22 eyes by more than one Snellen line ($P = 0.0391$, paired t-test), remained the same in 13 eyes, and decreased by more than one line in 2 eyes. This pilot study shows that cystotomy may have a role in the treatment of cystoid macular edema in diabetic patients.

Introduction

The role of vitrectomy in the treatment of diabetic macular edema with fibrous traction has been reported by Lewis [1] and Harbour [2].

We have performed vitrectomy on more than 300 cases with diabetic macular edema with attached posterior vitreous cortex, but without fibrous traction. In these eyes, there was no membrane to peel and we achieved posterior vitreous detachment by aspiration. Even in these cases without fibrous traction, vitrectomy was effective in reducing macular thickness and in improving visual acuity [3].

Retinal thickness was reduced firstly around the vascular arcade, but there remained focal edema around the fovea, as well as around leaky microaneurysms with convex shaped islands. Thus it took from 3 to 6 months or more for a complete elimination of edema around the fovea, and even longer for any visual improvement. In comparison to diffuse edema cystoid macular edema took longer to disappear [3].

In order to increase the success rate in eyes with cystoid macular edema we performed a direct approach with the assumption that there were no neuronal components at the vitreous side of the macular cyst. Furthermore, the observation that eyes with a recently developed macular hole obtained good visual acuity after surgical treatment, in spite of a rupture of the retina at the center of the macula undergirds our hypothesis.

Patients and methods

All patients in this study presented with cystoid macular edema as part of their diabetic retinopathy. In all cases the posterior vitreous cortex was attached to the retina. Eyes with media opacity were excluded.

In total we studied 22 eyes of 21 patients (8 female, 13 male). Age ranged from 50 to 73 years (average 59.9±6.9 years). 21 eyes were phakic, and one was pseudophakic. Corrected visual acuity before surgery ranged from 0.06 to 0.8. Suspected duration of CME ranged from 1 to 42 months (average 8.2 months).

Firstly, we performed a combined procedure with phacoemulsification and aspiration with intraocular lens implantation and pars plana vitrectomy, then induced posterior vitreous detachment.

Secondly, a direct approach was applied to eliminate the macular cyst with one of the following four procedures. Puncture and aspiration of the fluid was performed in 6 eyes. Incision along the cyst wall was made in 8 eyes. Excision of the cyst wall was made in 6 eyes (Figure 1). Lateral puncture with a subretinal canula through the retina was performed in 2 eyes. The puncture procedure had been developed by Dr. Yuichiro Ogura and the other three techniques are our innovations.

Fluid-air exchange was performed in 14 of 22 eyes, and Sulfurhexafloride (SF6) gas injection was performed in 11 of these 14 eyes. Gas tamponade was chosen in 4 eyes in order to close a peripheral retinal tear. In 10 eyes, it was performed to aid the elimination of fluid within macular cyst.

All operations were performed from September 1996 to December 1997. Follow up ranged from 3 up to 29 months (average of 13 months).

Results

Biomicroscopically cystoid macular edema was eliminated in 16 of 22 eyes during the follow up period. Ring-shaped residual edema was observed in one eye. The visual outcome is shown in Figure 2.

Corrected visual acuity was improved in 7 of 22 eyes by more than one line, remained the same in 13 eyes, and decreased by more than one line in 2 eyes. Visual improvement was statistically significant (P=0.0391, paired t-test).

Surgical complications were as follows. Intraoperative retinal tear formation was observed in 4 out of 22 eyes. Postoperatively, macular hole formation was seen in one eye, epimacular membrane formation in one eye, choroidal neovascularization in 2 eyes and recurrence of the macular cyst was seen in 3 eyes. The macular hole was closed by additional surgery with epiretinal

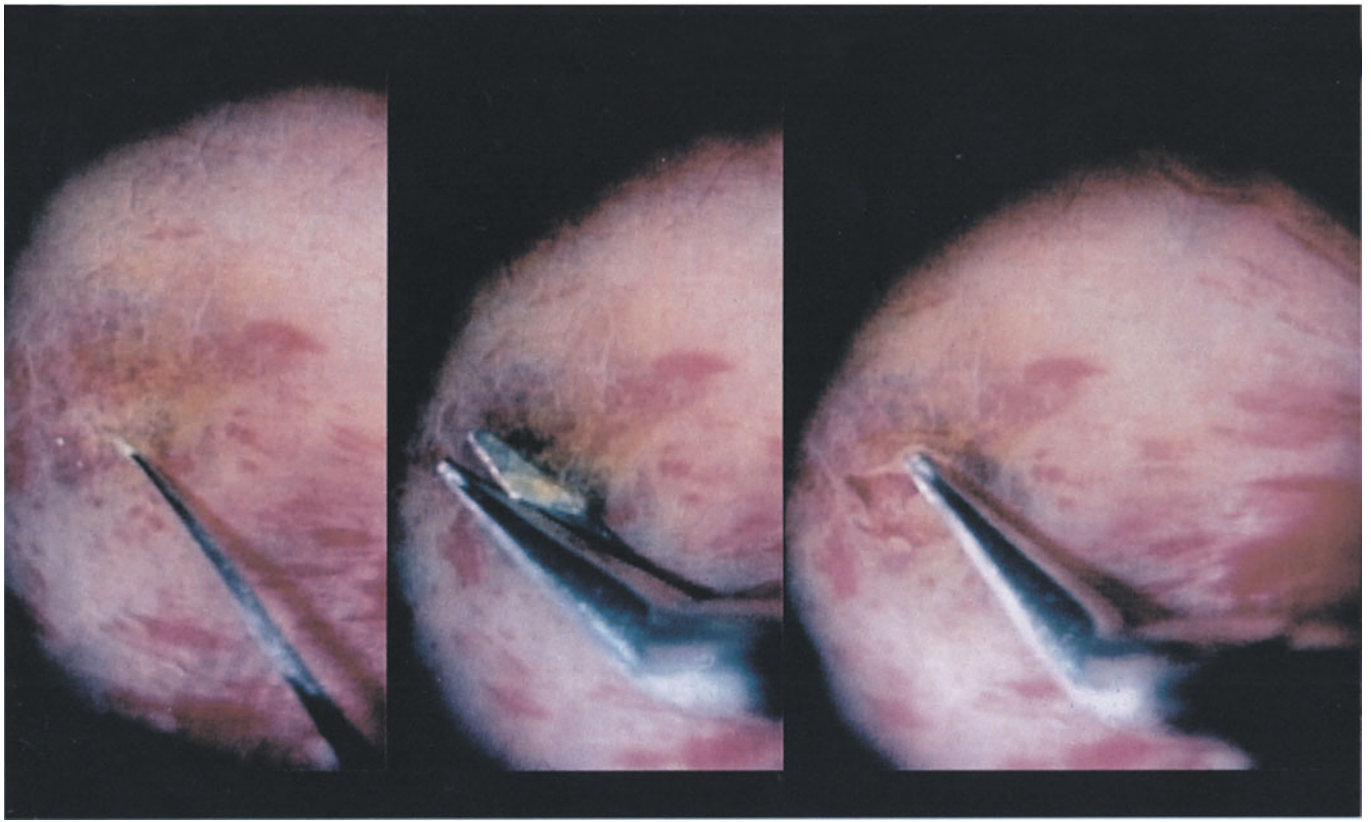

Figure 1. Procedure of cystectomy: Left: a subretinal pick is used to puncture the wall of the cyst. Center: The wall of the cyst is cut away from the macula by microscissors. Right: The remained cyst wall is removed by microscissors and the vitreous cutter.

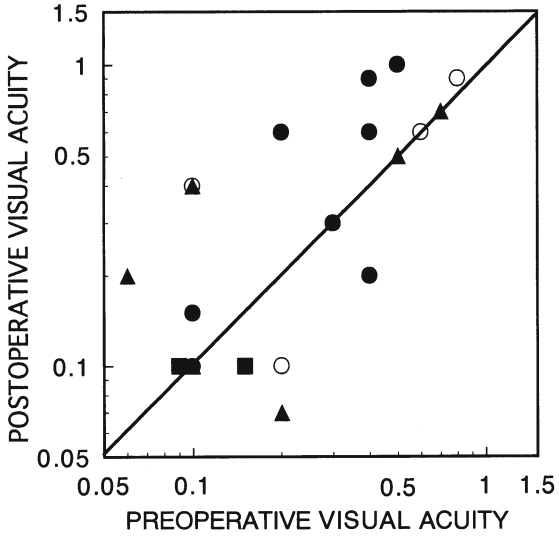

Figure 2. Visual outcome 6 months after vitrectomy. Closed circles denote eyes which underwent cyst incision (n = 8); closed squares represent eyes that underwent lateral puncture (n = 2); triangles denote eyes which underwent cyst excision (n = 6); open circles represent eyes that underwent puncture (n=6).

membrane peeling and gas injection. Two eyes which developed choroidal neovascularization had foveal deposit of hard exudate before surgery.

Discussion

We observed a slight improvement of vision following this procedure without any significant damage to the fovea. This reveals that this procedure has possibilities as one treatment modality for cystoid macular edema.

This pilot study is uncontrolled and we cannot conclude that our technique is more beneficial than achieving posterior vitreous detachment alone, but some observations suggest the distinct advantages of our procedure. We observed, e.g., a donut shaped residual edema in one case, a picture quite different from the residual edema seen after posterior vitreous detachment alone. Macular cysts disappeared during the surgery with aspiration in some cases.

The main advantage of combined surgery is to prevent surgical complications of vitrectomy and it was described in the previous review[4]. In eyes with diabetic retinopathy and/or cases older than 50 years, postoperative cataract formation is inevitable. Combined surgery is, designed to prevent such visual impairment, although the most valuable aspect of this procedure is

that it permits a complete vitrectomy. We named this procedure 'vitreous clearing' which reduces the risk of anterior hyaloidal fibrovascular proliferation. Furthermore we can find and close peripheral retinal tears much easier intraoperatively. With combined surgery and complete vitreous clearing, peripheral retinal tear formation may increase to some extent, but it is much easier to seal intraoperative retinal tears than to treat retinal detachment or proliferative vitreoretinopathy in the follow up. Additionally, we can perform endolaser photocoagulation on the peripheral retina as a prevention for neovascular glaucoma. In combined surgery, we also apply a self-sealing tunnel for the phacoemulsification and thus we can perform vitrectomy with a stable anterior chamber depth and without collapse of the globe and without iris prolapse.

Macular holes and epimacular membranes may be treatable by further surgery. On the other hand, choroidal neovascularization is another problem of macular surgery and it may seriously affect the postoperative visual acuity. But these eyes had previous foveal deposits. Choroidal neovascularization was observed after simple vitrectomy without macular manipulation in cases with macular deposits[5]. Therefore, choroidal neovascularization may have been induced either by the foveal deposits themselves or by the surgical intervention on the cyst.

Thus, visual outcome of surgery with incision or excision for macular cysts was valuable, but it is not entirely satisfactory. If surgery is carried out immediately, this procedure will affect on increasing of visual acuity.

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Vitrectomy for macular edema combined with retinal vein occlusion

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Abstract. This study was performed in order to evaluate the effect of vitrectomy in eyes with retinal vein occlusion associated with macular edema. Twenty-nine years eyes (27 patients) with branch retinal vein occlusion (BRVO), and 14 eyes (13 patients) with central retinal vein occlusion (CRVO) both associated with macular edema underwent phacoemulsification, intraocular lens implantation, pars plana vitrectomy and peeling of the posterior hyaloid membrane. Follow-up ranged from 12 to 32 months. Macular edema was reduced, and visual improvement was observed ($p < 0.0001$ in BRVO, $p = 0.0257$ in CRVO, paired t-test). Visual outcome was better in eyes with better visual acuity before surgery. Early vitrectomy may be recommended for retinal vein occlusion associated with macular edema.

Introduction

Previously, several authors have reported the effect of vitrectomy in eyes with diabetic macular edema [1]. Macular edema associated with retinal vein occlusion is another common cause of visual impairment in elderly people. In many of these eyes the posterior vitreous cortex is attached to the retina, and may be implicated in the pathogenesis of the edema. We report herewith the results of vitrectomy in eyes with macular edema combined with retinal vein occlusion.

Patients and methods

A total of 29 eyes from 27 patients with branch retinal vein occlusion (BRVO), and 14 eyes from 13 patients with central retinal vein occlusion (CRVO) were included in this study. The BRVO group contained 9 male (10 eyes) and 18 female (19 eyes) patients. Duration from the onset of BRVO to surgery was 1 to 25 months (average 9.5 months). Among 21 eyes from 29 eyes had received previous photocoagulation around the paramacular area. The CRVO group comprised 6 male (7 eyes) and 6 female (7 eyes) patients. Duration from the onset of CRVO to surgery was 1–35 months (average 2.8 months). Eight

eyes from 14 eyes had received previous photocoagulation in the paramacular area. In all the 43 eyes included in this study the posterior vitreous cortex was attached to the retina and no fibrous traction to the macula was observed during biomicroscopic examination.

We performed combined phacoemulsification and vitrectomy surgery to prevent surgical complications [2]. The aim of this operation was to achieve posterior vitreous detachment which was achieved by aspiration using a brush-backflush needle. Peripheral vitreous gel was shaved by scleral indentation.

All operations were performed from September 1994 to February 1997. Follow-up ranged from 12 up to 32 months (average 16.1 months).

Results

Macular edema was reduced rapidly, and visual improvement was observed. The preoperative fundus in a case of a 71-year-old female patient with macular edema combined with BRVO reducing visual acuity to 0.1 (Figure 1 top). The fundus of the same eye 6 months after surgery (Figure 1 bottom). Macular edema was reduced as judged by ophthalmoscopy, although the amount of hard exudate has increased. Postoperative visual acuity was 0.3. The overall visual outcome is shown in Figure 2. Visual improvement was observed until 12 months after surgery. After one year, visual acuity was maintained or slightly improved. These improvements were preceded by resolution of macular edema.

There was a greater overall improvement in visual acuity in eyes with BRVO than in CRVO ($p < 0.0001$ in BRVO, $p = 0.0257$ in CRVO, paired t-test). The time until complete reabsorption of macular edema had occurred was shorter in eyes which were operated on soon after the vein occlusion. $Y = 5.04-0.085 \log X$; $R^2 = 0.05$ (BRVO), $Y = 4.143-0.02 \log X$; $R^2 = 0.114$ (CRVO) (X = weeks from the onset of retinal vein occlusion to surgery, Y = months for resorption of macular edema). The time until complete reabsorption of macular edema had occurred was also shorter in eyes with better preoperative visual acuity. $Y = 2.13-2.704 \log X$; $R^2 = 0.212$ (BRVO), $Y = 2.46-1.579 \log X$; $R^2 = 0.112$ (CRVO) (X = weeks from the onset of retinal vein occlusion to surgery, Y = months for resorption of macular edema).

Better postoperative visual acuity was correlated with better preoperative visual acuity. $\log \alpha = 0.065 + 0.547 \log p$; $R^2 = 0.347$ (BRVO), $\log \alpha = 0.242 + 0.309 \log p$; $R^2 = 0.148$ (CRVO) (p = corrected visual acuity before surgery, α = corrected visual acuity 12 months after surgery).

Surgical complications included intraoperative retinal tear formation in 4 of the 43 eyes and postoperative macular hole formation in one eye.

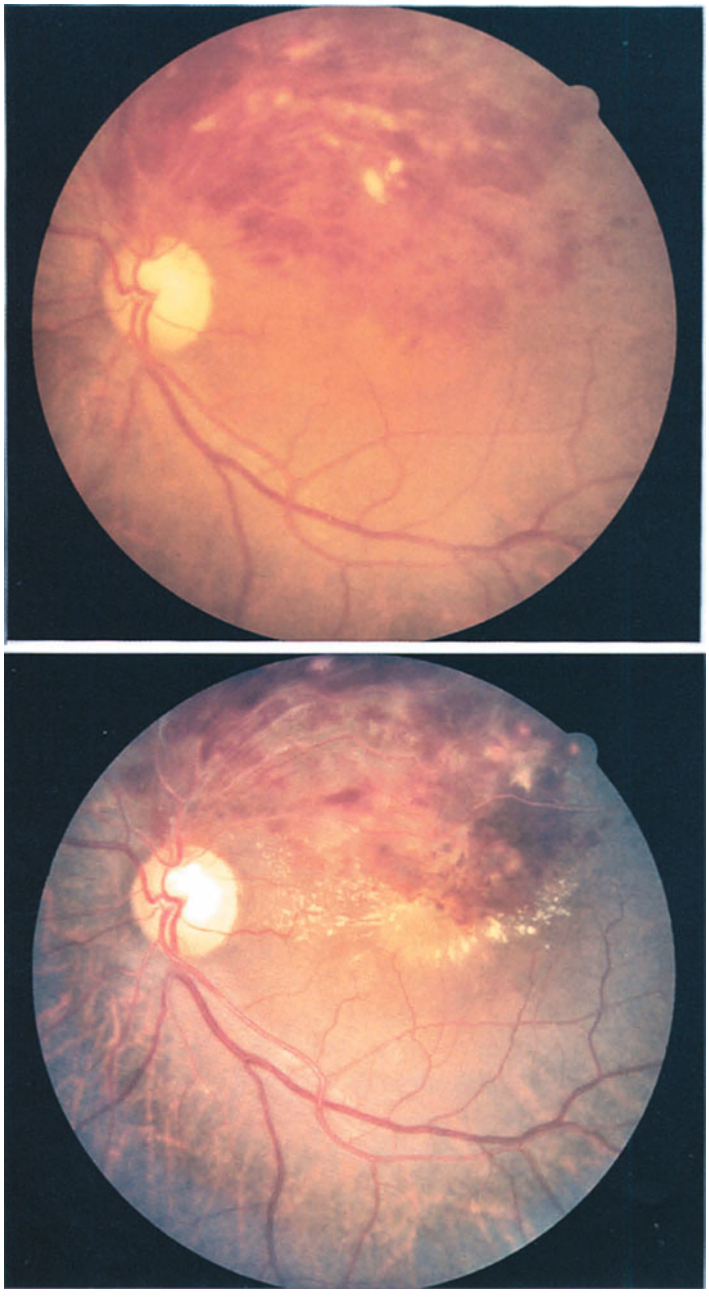

Figure 1. Top: Preoperative fundus photograph of a 71-year-old woman with a BRVO of superior temporal arcades reducing best corrected visual acuity to 0.1. Note to hemorrhage and exudate formation. Bottom: The same fundus 6 months after surgery, Macular edema was resolved although the amount of hard exudates has increased. Visual acuity has increased to 0.3.

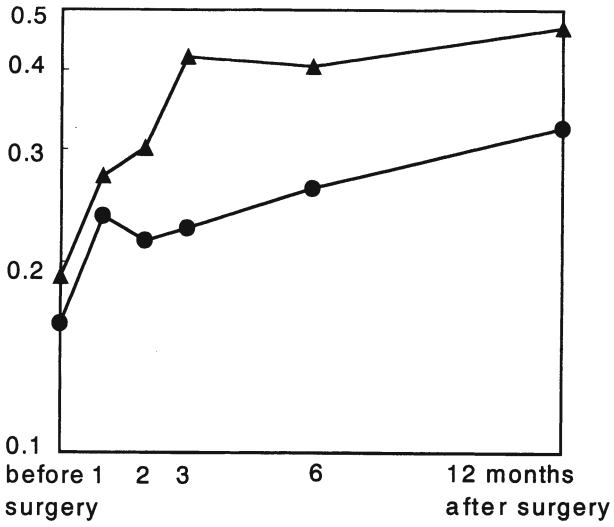

Figure 2. Evolution of the overall average of visual acuity of all included eyes during the 12 month follow-up period. Circles indicate 14 eyes with CRVO, and triangles indicate 29 eyes with BRVO.

Discussion

Vitrectomy was effective in eliminating macular edema in eyes where the edema was due to a retinal vein occlusion. The increase of hard exudates which was observed after surgery may be the consequence of rapid fluid absorption. The same phenomena was also noticed in cases with diabetic macular edema. A similar relationship between edema and vitreous traction as is found in eyes with diabetic macular edema, may exist in our cases. Thus, vitrectomy may similarly liberate the retina from tangential vitreous traction. The time until resorption of edema was shorter in eyes which had a shorter duration of retinal vein occlusion. In eyes with better preoperative visual acuity, macular edema resolved faster, both in BRVO and CRVO. Improvement in visual acuity was better in eyes with BRVO than in eyes with CRVO. This may be the result of more severe damage in the macula of eyes with CRVO. Visual outcome was also better in eyes which had a higher visual acuity before surgery. Our results suggest that vitrectomy may be effective in reducing macular edema and that a less damaged macula may obtain better postoperative function after the resolution of macular edema. In conclusion early surgery has been recommended once vein occlusion has occurred.

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Pars plana vitrectomy in diabetic macular edema

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Abstract. *Purpose*: To ascertain the association between the improvement of diabetic macular edema and increased visual acuity after pars plana vitrectomy. *Methods*: From January 1994 to December 1996 we prospectively studied 18 patients (18 eyes, 7 women and 11 men, mean age 52 years, range 37–68) with type II diabetes and clinically significant macular edema. One group was composed of 9 patients presenting diffuse macular edema (DME); a second group with 9 patients presented cystoid macular edema (CME). All patients underwent pars plana vitrectomy. *Results*: Preoperative Snellen visual acuity was 20/143 in DME and 20/441 in CME. In both groups vision increased to 20/136 and 20/205, respectively, postoperatively. For the DME this difference was statistically significant ($p<0.05$) at 1 month after the surgery, but vision decreased again after 10 months reaching preoperative values. *Conclusions*: Our results suggest that pars plana vitrectomy for diabetic macular edema may increase visual acuity in diffuse macular edema, although this increase is only short lived.

Key words: vitrectomy, diabetes, macular edema, visual acuity

Introduction

Macular edema due to diabetic microangiopathy is one of the principal causes of low visual acuity in diabetic patients. Pars plana vitrectomy has been described as a powerful tool to treat diabetic macular edema [1–4]. However, the role of vitreomacular adherence in the pathogenesis and the evolution of diabetic macular edema is not entirely clear. In order to elucidate these mechanisms better, we studied two distinct groups of patients with either diffuse or cystoid diabetic macular edema.

Patients and methods

From January 1994 to December 1996 we prospectively studied 18 patients (18 eyes, 7 women and 11 men, mean age 52 years, range 37–68) with type II diabetes and clinically significant macular edema. Inclusion criteria were vitreomacular adherence as shown by ultrasonography, vitreomacular adherence as shown by biomicroscopy, laser treatment completed at least 4 months

previously, diffuse macular edema shown on fluorescein angiography, no media opacities. Diabetes had to be well controlled with serum values of Hb1Ac lower than 8 mg/l. We excluded patients who had other ocular diseases, kidney problems or other diseases that might induce macular edema, and patients who had had incomplete laser treatment of their diabetic retinopathy. Patients were allocated into two different groups. One group was composed of 9 patients presenting diffuse macular edema (DME); a second group with 9 patients presented cystoid macular edema (CME). All patients underwent standard pars plana vitrectomy with posterior hyaloid delamination using the flute needle or a peeling hook [3].

At baseline the following exams were performed: visual acuity (ETDRS charts), slitlamp biomicroscopy, ultrasonography, stereo photographs of the posterior pole, fluorescein angiography. At the 1 month follow-up visit the same exams were repeated. Each patient was examined every 2 months for 16 months. All 18 patients had type II diabetes. 7 were women and 11 men, the mean age being 52±8 years (range 37–68). In 7 patients the diabetic retinopathy was proliferative, in 11 pre-proliferative. The first group was composed of 9 patients presenting diffuse macular edema (DME). Mean age 49±4 years. The second group with 9 patients presented cystoid macular edema (CME) (mean age 54±10years). The details of these patients are seen in Table 1.

Results

There were no intraoperative complications during the pars plana vitrectomy. Posterior vitreous delamination was achieved in all patients. During the postoperative phase patient 3 of the group with CME developed a reitinal detachment with a small peripheral break. Patient 3 of the group with DME, and patients 1, 3, 5 and 7 of the group with CME developed lens opacities which affected visual acuity, and these 4 patients were eventually excluded from the study.

Preoperative Snellen visual acuity was 20/143 in DME and 20/441 in CME. In both groups vision increased to 20/136 and 20/205, respectively, postoperatively. For the DME this difference was statistically significant (Repeated measures Anova, $p<0.05$) at 1 month after the surgery, but vision decreased again after 12 months reaching preoperative values at the last follow-up visit. Visual acuity never increased significantly in the group with CME.

Table 1. Patients and anatomical findings

Patients	Age	Sex	Eye	Retinopathy	Macular edema	V.A. pre op.	Anatomical findings
1	45	M	L	Proliferative	Diffuse	20/200	Reduction of fluo. leakage
2	52	F	L	Pre-proliferative	Diffuse	20/100	Stability
3	46	F	L	Pre-proliferative	Diffuse	20/200	Lens opacity
4	53	F	R	Proliferative	Diffuse	20/50	Stability
5	53	M	R	Pre-proliferative	Diffuse	20/40	Stability
6	44	M	R	Pre-proliferative	Diffuse	20/100	Stability
7	48	F	L	Pre-proliferative	Diffuse	20/20	Stability
8	55	M	L	Pre-proliferative	Diffuse	20/200	Reduction of fluo. leakage
9	48	M	L	Pre-proliferative	Diffuse	20/200	Reduction of fluo. leakage
Average	49.33					20/143.33	
SD	4					70	
Patients	Age	Sex	Eye	Retinopathy	Macular edema	V.A. pre op.	Anatomical findings
1	49	M	L	Pre-proliferative	Cystoid	20/500	Lens opacity
2	48	M	R	Proliferative	Cystoid	20/200	Reduction of fluo. leakage
3	57	F	L	Proliferative	Cystoid	20/500	Retinal detachment
4	54	M	R	Pre-proliferative	Cystoid	20/63	Stability
5	56	M	L	Proliferative	Cystoid	20/500	Lens opacity
6	68	M	L	Proliferative	Cystoid	20/500	Stability
7	37	F	L	Proliferative	Cystoid	20/500	Lens opacity
8	67	M	R	Pre-proliferative	Cystoid	20/200	Stability
9	51	F	R	Pre-proliferative	Cystoid	20/500	Stability
Average	54.11					20/444.44	
SD	9.60					142.40	

Discussion

Despite recent reports, our study showed no longterm positive effect of pars plana vitrectomy with vitreal delamination in the treatment of diabetic macular edema. The short-lived improvement in visual acuity seen in the group with DME one month after surgery did not translate into a longterm increase in visual acuity at the subsequent follow-up visits. It appears, therefore, from our data, that only patients with diffuse macular edema respond favourably

to pars plana vitrectomy in the short term. This may be explained by the fact that vitreomacular traction is temporarily relieved, but the subsequent deterioration of the microangiopathy will nevertheless lead to a deterioration of the maculopathy in the long run. The inability of vitrectomy to improve visual acuity in patients with CME may be due to irreversible damage to the retina which has occurred following widespread intraretinal fluid accumulation.

References

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