European University Professors of Ophthalmology

EUPO Course 2011

June 3-4, 2011 - GENEVA, Switzerland

UVEITIS and GLAUCOMA

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EUPO

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June 3-4, 2011 - GENEVA, Switzerland

UVEITIS and GLAUCOMA

Uveitis: organizer Carlos Pavesio
Glaucoma: organizer Carlo E. Traverso

Dear colleagues,

It is a great pleasure for us to welcome you to Geneva, host of the 2011 Course of the European Professors of Ophthalmology (EUPO). This year, Uveitis is one of the focus of the course and I am happy that so many experts in this field have agreed to join us for what promises to be an exceptional day. The course will cover basic and clinical aspects, from the anterior to the posterior segment of the eye. The speakers will bring their personal experience to their lectures and this will reflect different practices across Europe.
I am certain the wide range of topics and the practical information of this course will give you invaluable guidance for your daily practice.
I hope you will all enjoy the course and the beautiful and friendly city of Geneva.

Mr Carlos Pavesio
Uveitis EUPO Course Organiser

The sequence of the EUPO courses

2011	Geneva	Uveitis & Glaucoma
2010	Athens	Retina
2009	Amsterdam (SOE)	Cornea, Conjunctiva and Refractive surgery
2008	Geneva	Neuro-ophthalmology and strabismus
2007	Vienna (SOE)	Glaucoma and uveitis
2006	Ghent	Retina
2005	Berlin (SOE)	Cornea
2004	Nijmegen	Neuro-ophthalmology and strabismus
2003	Madrid (SOE)	Glaucoma and uveitis
2002	Erlangen	Retina
2001	Istanbul (SOE)	Cornea
2000	Leuven	Neuro-ophthalmology and strabismus
1999	Stockholm (SOE)	Glaucoma and uveitis
1998	Amsterdam (ICO)	Chorioretina
1997	Budapest (SOE)	Cornea, conjunctiva, lids, orbit
1996	Athens	Neuro-ophthalmology and strabismus
1995	Milano (SOE)	Uveitis, lens, glaucoma
1994	Montpellier	Retina
1993	Santiago de Compostella	The external eye
1992	Brussels (SOE)	Neuro-ophthalmology and strabismus
1991	Torino	Uveitis, lens, glaucoma
1990	Bonn	Chorioretina
1989	Leuven	The external eye and orbit
1988	Nijmegen	

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2006
Retina

2007
Uveitis

2008
Neuro-Ophthalmology and Strabismus

2009
Cornea, Conjunctiva and Refractive surgery

2010
Retina

PROGRAMME EUPO 2011 - Friday, June 3

Uveitis: the basics and beyond

Moderator: Carlos Pavésio, United Kingdom

PROGRAMME EUPO 2011 - Friday, June 3

Uveitis: the basics and beyond

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Notes

Welcome to the EUPO Party!

Venue: Kiosque de Bastion, Friday, June 3, 2011

You are a speaker or have registered to attend the EUPO Course 2011 in Geneva. The registration fee for the EUPO Course includes the EUPO Party.

The party starts at 18.15, 3 June, 2011 – immediately after the last session. Buses will take you from Palexpo directly to the party.

The party will take place at the Kiosque de Bastion, located in the Geneva city centre.

It will be an evening filled with food, drinks and music allowing the opportunity for social interaction and enjoyment between EUPO speakers and boardmembers and all EUPO delegates!

Don't forget to bring your ticket received upon registration.

Dress Code: Smart/Casual

Welcome!

PROGRAMME EUPO 2011 - Saturday, June 4

Glaucoma: from scientific evidence to clinical practice

■ 08.15 - 09.45 **Section 1: Diagnosis and fate of POAG**

Moderators: Carlo E. Traverso, Italy / Thierry Zeyen, Belgium

Introduction
Carlo E. Traverso, Italy

Function
Francisco Goñi, Spain

Structure
Hans Lemij, The Netherlands

Function and structure agreement
Paul Artes, United Kingdom

Case finding
Fotis Topouzis, Greece

Rate of visual field progression
Ingeborg Stalmans, Belgium

Life expectancy and quality of life
Norbert Pfeiffer, Germany

■ 10.15 - 11.45 **SOE congress, Opening Ceremony**

■ 11.45 - 12.00 **Break and Exhibition / Electronic posters**

■ 12.00 - 13.00 **Special Session: Stuart Fine, United States**
Lucentis vs Avastin for wet AMD. The CATT results in a European context

■ 13.00 - 13.30 **Break and Exhibition / Electronic posters**

■ 13.30 - 14.15 **Key Note Lecture: Anders Heijl, Sweden**
Lessons from the early manifest glaucoma trial

PROGRAMME EUPO 2011 - Saturday, June 4

Glaucoma: from scientific evidence to clinical practice

■ 14.30 - 16.00 Section 2: Management 1

Moderator(s): Carlo E. Traverso, Italy

Likelihood of visual handicap from glaucoma
Ananth Viswanathan, United Kingdom

Goals of treatment and IOP lowering medications
John Salmon, United Kingdom

Non-IOP lowering: nutraceuticals and neuroprotection
Leo Schmetterer, Austria

Compliance/persistence
Anton Hommer, Austria

Early glaucoma and OH: to treat or not to treat?
Stefano Miglior, Italy

■ 16.30 - 18.00 Section 3: Management 2

Moderator(s): Carlo E. Traverso, Italy

Laser for POAG
Johan Thygesen, Denmark

Surgery for POAG
Franz Grehn, Germany

Cataract surgery in glaucoma
Carlo E. Traverso, Italy

Postoperative Bleb management: the key to success
Thierry Zeyen, Belgium

Cost of diagnosis
Anja Tuulonen, Finland

Angle closure is not so rare in Europe
Giorgio Marchini, Italy

Closing remarks
Carlo E. Traverso, Italy

Notes

Immunologic mechanisms

Gerhild Wildner, Germany

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Immunobiology and ocular inflammatory diseases

Autoimmune uveitis is mediated by T helper cells recognizing intraocular antigens. The T cells secrete cytokines and chemokines, which attract inflammatory cells such as macrophages and granulocytes. These inflammatory cells have the capacity to destroy the delicate structures of the eye, leading to decreased vision. The role of autoantibodies/B cells is not clear, so far it is assumed that they do not play a key role in the pathogenesis of uveitis.

Antigen recognition, B and T lymphocytes

While B cells can recognize very complex antigens (proteins, carbohydrates, nucleic acids, nitrophenyl etc.) with their immunoglobulin receptors (membrane-anchored antibodies), T cells only recognize peptides "processed" from proteins by antigen-presenting cells ("professional"APC: dendritic cells, macrophages or B cells) and presented on MHC antigens. CD8+ T cells with mainly cytotoxic functions (but also including regulatory cell populations) see antigen peptides derived from intracellular proteins (e.g. viruses, intracellular bacteria) presented on MHC class I molecules (HLA-A, -B, -C). CD4+ T cells include T helper cells and also a regulatory T cell population (CD4+CD25+). CD4+ T cells recognize preferentially peptides from extracellular antigens presented on MHC class II molecules (HLA-DQ, -DR, -DP). The CD4+ T cells provide help for other T cells (e.g. CD8+ cytotoxic T cells), if they belong to the Th1 type, or B cell help, enhancing antibody production and isotype switch, if they are Th2 type cells. Th1 and Th2-type cells can be distinguished by the pattern of cytokines they secrete: while Th1 cells secrete interleukin-2 (IL-2), interferon-gamma (IFN-!) and tumor necrosis factor-alpha (TNF-"), the main cytokine produced by Th2 cells is IL-4.

Autoimmune uveitis is mediated by T-helper cells, presumably of the Th1 type. This raised the question why multiple HLA class I antigens, such as B27, B51 and A29 are highly associated with certain uveitis entities, although uveitogenic Th1 cells need their antigen presented on HLA class II molecules. The phenomenon of "antigenic mimicry", described at the end of this section, could offer an explanation.

The immune privilege of the eye

To preserve the eyes from destructions by the immune system, mechanisms have developed that prevent invasion of non-activated lymphocytes and potentially dreadful immune components. The so-called "immune privilege" is mediated by

1. The blood-retina-barrier
2. ACAID = anterior chamber-associated immune deviation

The blood-retina-barrier (BRB)

Tight junctions of the intraocular endothelia prevent transmigration of non-activated leucocytes,

such as T- and B-cells, NK-cells, macrophages and granulocytes. Furthermore, the BRB is impermeable for macromolecules such as antibodies, complement and coagulation factors.

ACAID

ACAID defines the immune privilege of the anterior chamber, but there is a retinal immune privilege as well.
Antigens within the eye normally do not activate an immune response, but rather induce tolerance. Intraocular antigens (naturally occurring or experimentally introduced) are transported to the spleen, where antigen-specific tolerance is generated. Special dendritic cells/macrophages (F4/80+) localized in iris and ciliary body can only induce a tolerogenic, but no defensive immune response.
Ocular antigens induce regulatory cells (T cells, NK cells) and production of non-complement-fixing antibodies.
Furthermore, iris and ciliary body secrete suppressive factors, such as TGF-β, IL-10, α-MSH and others.
Besides preventing intraocular inflammation, ACAID also helps to accept corneal grafts.

Why do we get uveitis in spite of the immune privilege of the eye?

Destruction of the blood-retina-barrier (e.g. by penetrating injury, tumors with invasive growth) can enable the invasion of non-activated T cells for in situ activation to ocular antigens (sympathetic ophthalmia: injury of one eye leads to autoimmune attack of the other eye).

The blood-retina-barrier as well as ACAID can be overcome by activated leucocytes. They are enabled to penetrate the BRB and are not bothered by the suppressive factors in the eye. However, they have to be activated specifically for intraocular antigens, which are usually sequestered and not accessible to the immune system, as long as the BRB is intact. In case of infectious uveitis the respective pathogen has normally been seen by the immune system in the periphery. Thus, activated lymphocytes with specificity for the pathogen can invade the eye to attack the virus or bacteria. For “autoimmune” uveitis we postulate antigen crossreactivity, “mimicry” of an antigen activating the immune system in the periphery and an intraocular antigen. Those peripherally activated T cells can cross the BRB and will find an antigen in the eye that resembles the antigen of their original activation. Local reactivation and subsequent secretion of inflammatory cytokines will initiate inflammation such as uveitis. Those “mimotopes” can be provided by environmental antigens such as pathogens or even nutritional antigens (e.g. casein from bovine milk).

A peptide derived from the sequence of HLA-class I molecules can mimic a peptide from retinal S-Antigen. This HLA-class I-derived peptide is found in the sequence of many HLA-class I antigens, especially in those associated with uveitis. This HLA-class I peptide can be presented by HLA-class II molecules to Th1 cells and probably mimic also other peptides besides that of S-Antigen, e.g. from pathogens. In this case, the HLA-class IB antigen has turned its function from an antigen-presenting element to an antigen.

Fig. 1: Specific autoimmune response leading to inflammation

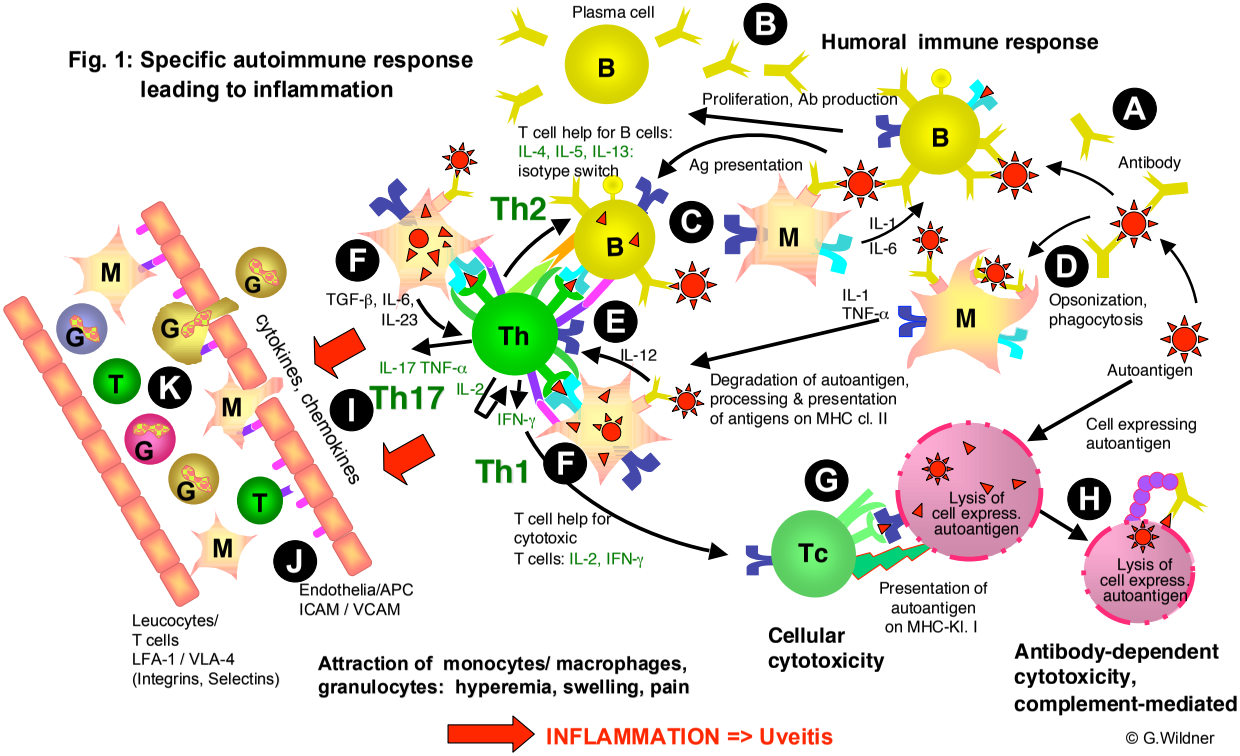

Fig. 1: Specific autoimmune response leading to inflammation

(A) An autoantigen is recognized and bound by antibodies. This leads to cross-linking of the surface immunoglobulins (antibodies, Ab) on the respective antibody-producing B cell. Here, the surface antibodies serve as B-cell receptors. Antigen binding stimulates the B cell to proliferate and to further mature to a plasma cell (B). B cells can also internalize the antigen, which is bound by their surface Ab, process it, and present peptides from this antigen on their MHC class II molecules, to seek T cell help (C). The help provided from a Th2 cell by cytokines such as IL-4, IL-5, and IL-13 enables the B cell to undergo isotype switch and subsequently produce antibodies of another IgG, IgA, or IgE type.

Antibody-bound or „opsonized" antigen is easily sensed by macrophages via their surface Fc receptors (D); they subsequently phagocytose the complex. The bound antigen is also processed and presented to T cells as peptides (E). By secreting certain cytokines during antigen presentation to a naive T cell, antigen-presenting cells can determine the T-cell type (Th1 by IL-12 or Th17 by IL-6 and TGF-β) (F). These T cells can help cytotoxic T cells (if they are Th1 cells) to support lysis of cells that present intracellular antigen on their surface MHC class I molecules, a mechanism normally used to eliminate virus-infected cells but also found in autoimmunity (G). Cell lysis can also be obtained by binding of antibodies and complement factors (antibody-dependent cytotoxicity) (H).

T-helper cells of all three types, Th1, Th2, and Th17, can recruit inflammatory cells such as granulocytes and monocytes/macrophages to the site of their antigen recognition, no matter if the antigen is a pathogen, an allergen, or an autoantigen. This recruitment is mediated by cytokines and chemokines (chemotactic cytokines) (I), which induce upregulation of cell adhesion molecules („CAMs") on neighboring vascular endothelia (J) used to attract and catch leukocytes from the circulation (K). They finally migrate through the endothelium into the tissue to fight against pathogens (or, in autoimmune diseases, against the own tissue) with their highly effective „chemical weapons", causing the typical signs of inflammation.

Prof. Gerhild Wildner, PhD,
Clinic of the Ludwig-Maximilians-University,
Dept. of Ophthalmology, Section of Immunology,
Mathildenstr. 8, 80336 Munich, Germany
(Gerhild.Wildner@med.uni-muenchen.de)

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in Gupta A, Gupta V, Herbort CP, Khairallah M (Eds). Uveitis.
Jaypee Brothers Medical Publishers, New Delhi, 2009, 232-245.

Electrophysiology and Inflammatory Disease

Graham E Holder

INTRODUCTION

The objective information provided by electrophysiological assessment can have a significant effect on the diagnosis and management of the patient with retinal dysfunction related to inflammatory disease. Signs and symptoms may be poor indicators of the severity or even nature of the disease, and electrophysiology not only allows a direct assessment of function and establishes a baseline against which the efficacy of treatment can be judged, but can also, by demonstrating objectively the degree and nature of dysfunction, assist in the initiation of treatment. Given the potential toxicity of some of the treatment options, it is of value to have an objective determinant of retinal dysfunction and its response to treatment.

THE TESTS

Prior to a discussion of the specific findings in inflammatory disease, a short introduction to the tests and signal origins in electrophysiology may assist the reader's understanding. The International Society for Clinical Electrophysiology of Vision (ISCEV) has published Standards or Guidelines for the performing of the main tests; readers are referred to those documents and those practising electrophysiology are strongly urged to incorporate the ISCEV Standards into their routine protocols.

The electroretinogram (ERG) is the mass electrical response of the retina elicited by luminance stimulation. ERGs are recorded using corneal electrodes with stimuli delivered by a Ganzfeld bowel to enable uniform whole field illumination; the Ganzfeld not only provides flash stimulation but also a diffuse background for photopic adaptation. The reference electrodes are positioned at the ipsilateral outer canthi if a bipolar contact lens electrode is not used (they have a built-in reference). ISCEV facilitates standardisation across laboratories by defining a standard flash as 1.5-3.0 cd.s.m^{-2}. The response to this flash under scotopic conditions, with full pupil dilation, is the maximal or mixed response (Figure 1). This response is often regarded as a "typical" ERG, but although there is a cone contribution, this maximal response is dominated by rod driven activity. The "single bright white flash (SBWF)" ERGs herein were recorded to an ~11.0 cd.s.m^{-2} flash better to view the a-wave, as "suggested" in the most recent ISCEV ERG standard.[1] The initial 8-10 ms of the a-wave reflects hyperpolarisation of the (mainly) rod photoreceptors, and the slope of the a-wave can be related to the kinetics of phototransduction.[2] The b-wave is generated postreceptorally in relation to bipolar cell function (ON in the rod system; ON and OFF in the cone system). The oscillatory potentials, the small wavelets on the b-wave, are probably generated in relation to amacrine cell activity. When the standard flash is attenuated by 2.5 log units the flash intensity is below the cone threshold and a rod-specific b-wave is obtained which arises in the rod ON bipolar cells.

Cone system ERGs are obtained under photopic conditions, following a standardised period of photopic adaptation, using both single flash and 30 Hz flicker stimulation superimposed upon a rod-saturating back-

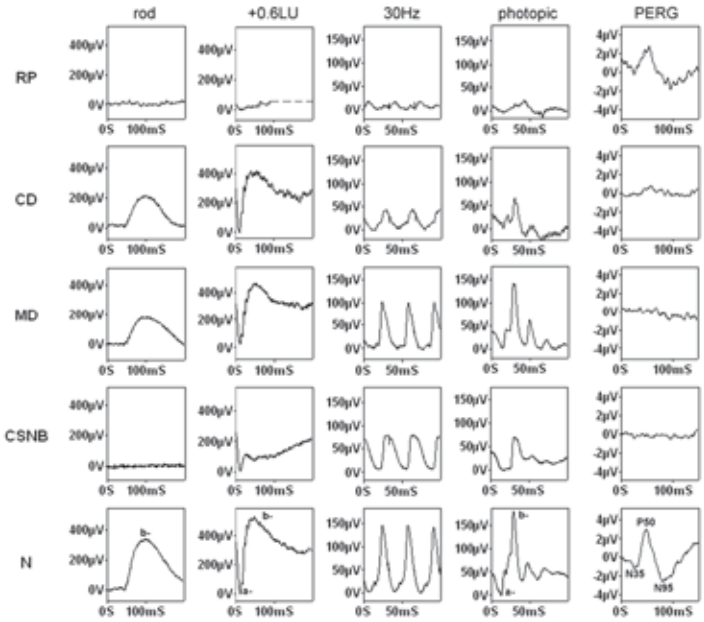


Figure 1: Normal ERGs and representative examples of disease. RP – retinitis pigmentosa (rod-cone dystrophy). ERGs show global reduction and delay, rod ERGs more than cone ERGs. The normal pattern ERG (PERG) demonstrates macular sparing. The dotted line replaces blink artefact; CD – cone dystrophy. Photopic single flash and cone flicker ERGs are subnormal and delayed. PERG is reduced. Rod system ERGs are normal; MD – macular dystrophy. Full field ERGs are normal. PERG is almost undetectable; CSNB – congenital stationary night blindness (complete form, NYX mutation). Rod specific ERG is undetectable. Maximum ERG is of (electro-) negative waveform indicating dysfunction post-phototransduction; cone ERGs show changes characteristic of cone ON– pathway dysfunction with cone OFF – pathway sparing. PERG shows marked macular dysfunction; N – normal

ground (17-34 cd/m^2). The poor temporal resolution of the rod system, in addition to the presence of a rod-suppressing background, enables a cone-specific waveform to be recorded using the 30 Hz stimulus. This response is perhaps the more sensitive measure of cone dysfunction, and is generated at an inner retinal level,[3] precluding localisation of any dysfunction either to the cone photoreceptors or inner nuclear layer. Better localisation within the retina is obtained with the single flash photopic ERG. Although there is a contribution from the hyperpolarising (OFF) bipolar cells to the photopic a-wave,[4] the photopic a-wave seems at least partly to be generated in relation to cone photoreceptor function. To a short flash stimulus, ON and OFF activity within the photopic system is effectively synchronised and the cone b-wave reflects both ON- and OFF bipolar cell function. The retinal ganglion cells do not significantly contribute to the flash ERG.

The ERG is a mass response and is therefore not significantly affected when dysfunction is confined to small retinal areas. This also applies to macular dysfunction; despite the high photoreceptor density, an eye with disease confined to the macula has normal ERGs (Figure 1). Separation of the cone ON and OFF

pathways can be achieved using a long duration stimulus with a photopic background.[5,6] The stimulus is usually generated either via a shutter system or by using light emitting diodes. For a full discussion of the origins of the ERG the reader is referred to Frishman.[7]

The pattern electroretinogram (PERG) is usually evoked by a reversing black and white checkerboard and is the response of central retina to an iso-luminant stimulus. It allows both a measure of central retinal function, and, because of its cellular origins, an evaluation of retinal ganglion cell function. It is thus important in the electrophysiological differentiation between optic nerve and macular dysfunction.[8] The PERG is recorded without mydriasis using non-contact lens electrodes in contact with the cornea or bulbar conjunctiva to preserve the optics of the eye. Suitable electrodes are the gold foil,[9] the DTL[10] and the H-K loop electrode.[11] The reference electrodes must be at the ipsilateral outer canthi to avoid the contamination from the cortically generated VEP that occurs if forehead or ear reference electrodes are used.[12]

The PERG with a stimulus reversal rate of < 6 reversals/sec has 2 main components: P50 at approx. 50 msec and a larger N95 at 95 msec.[13] P50 amplitude is measured peak to peak from the trough of the early negative N35 component, and the amplitude of N95 is measured to trough from the peak of P50 (Figure 1). The P50 peak time is also measured, but N95 peak time is not usually measured. N95 is a contrast-related component arising in the retinal ganglion cells. It is likely that approximately 70% of P50 is generated in the ganglion cells, but the remaining 30% is not related to spiking cell function and may be generated more distally.[14] The exact origins are yet to be ascertained. As the P50 component is "driven" by the macular photoreceptors, P50 amplitude can act as an objective measure of macular function. An analysis time of 150 msec or greater is usually used for the PERG, with approximately 150 averages per trial. The low amplitude of the PERG demands stringent technical controls during recording; these are addressed elsewhere.[15] Binocular stimulation and recording is usually performed so that the better eye maintains fixation. If there is a history of squint it is necessary to use monocular recording. P50 is very sensitive to optical blur, and appropriate refraction should be used during recording. PERG amplitude is also highly dependent upon stimulus contrast; the stimulus recommended by ISCEV is a high contrast black and white reversing checkerboard with ~40 minute checks in a 10-16 degree field.

Macular function is also assessed using multifocal electroretinography (mfERG) which, in addition, provides spatial information regarding central retinal cone system function. The stimulus consists of multiple scaled hexagons displayed on a television monitor, each of which flashes on with its own pseudo-random binary sequence (an M-sequence). Complex mathematics derives the individual responses that relate to each individual hexagon, generating multiple cone system ERG waveforms from a single recording electrode. The mfERG can be of use in disturbances of macular function and to assess the extent of central retinal involvement in generalised retinal disease, but is highly susceptible to poor fixation, and the ability of a patient accurately to maintain good fixation throughout the recording session is a pre-requisite to obtaining clinically meaningful data. In the author's laboratories, mfERG is used in association with the full-field ERG and the PERG. Guidelines for the performing of mfERG have been published by ISCEV.[16]

EFFECTS OF PATHOLOGY

Disturbances of photoreceptor function, in relation to the origins of the bright flash ERG a-wave, result in abnormalities of the a-wave. In general terms, there is an association between loss of function and loss of amplitude, but generalised dysfunction is likely to show changes in response timing. The bright flash dark-adapted ERG is a rod dominated response, and dysfunction confined to the cone system may only show changes in relation to the photopic ERGs, i.e., the 30 Hz flicker response and the single flash photopic ERG. Inner retinal dysfunction, where the defect occurs post-phototransduction, spares the bright flash a-wave but affects the b-wave, such that the b-wave is of lower amplitude than a normal a-wave. Such a waveform, where the ERG is dominated by the negative-going a-wave is known as a "negative" or "electronegative" ERG. Abnormalities of the pattern ERG reflect a disturbance of macular function. Figure 1 demonstrates a set of normal ERGs and ERGs from patients with retinitis pigmentosa (rod-cone dystrophy), cone

dystrophy, macular dystrophy and X-linked congenital stationary night blindness.

CLINICAL APPLICATIONS

BIRDSHOT CHORIORETINOPATHY

Birdshot chorioretinopathy (BCR) is a chronic, usually bilateral, inflammatory disorder characterised by multiple discrete cream coloured areas of subretinal hypopigmentation, cystoid macular oedema (CMO), vitritis, and retinal vasculitis.[17-19] Disc oedema may occur. Vascular attenuation and optic disc pallor may be present in end stage disease. The creamy white areas of depigmentation may not be seen in the early stages, and, when present may be confluent or may radiate outwards from the optic disc. There may be atrophic changes in the latter stages of the disease.[20] Most patients present to the ophthalmologist with an insidious onset of floaters; this may be followed by visual acuity reduction, often related to the presence of CMO. Other common symptoms include nyctalopia, photopsia, constriction of the visual field and defective colour vision. BCR has a very strong association with the HLA-A29 antigen[21-24] and most affected patients are HLA-A29 positive.[25] There are limited histopathological data available, but a recent report of histopathology described lymphocytic aggregations in the choroid, retinal vasculature and optic nerve head.[26] Similar findings have been reported in HLA-A29 transgenic mice.[27]

Unfortunately, BCR has an unpredictable and recurrent clinical course, making management decisions difficult. Indications for treatment are not always clear, and further difficulties occur when trying to assess the influence of therapeutic intervention on visual outcome. Currently, there is little consensus on the appropriate methods for assessing the efficacy of treatment. Visual acuity (VA) does not provide an assessment of generalised retinal function, and is therefore not satisfactory.[28-29] Other clinical parameters, such as the degree of intraocular inflammation, do not always accurately reflect the degree of retinal dysfunction. The objective information provided by electrophysiology may thus greatly facilitate patient care.

Early reports of electroretinogram (ERG) changes in BCR described inner retinal dysfunction in the form of an electronegative ERG;[30] there is eventual additional outer retinal involvement.[29-31] It has subsequently been reported that marked ERG changes may occur when symptoms are mild or even absent, and that ERG can determine when normal retinal function has been restored consequent upon treatment.[32] The most common abnormality is an increased peak time of the 30 Hz flicker ERG; marked delay can occur in the absence of any amplitude reduction, and indeed amplitudes can even be higher in the (more) affected eye. Such an observation, although the mechanism is not understood, can also occur in other inflammatory disorders. It has become our view that electrophysiological investigation not only provides objective criteria for the efficacy of treatment, but can also be an indicator for the initiation or restitution of treatment. It is assumed, although no direct supporting evidence exists, that restoration of normal function to an abnormally functioning retina is beneficial to the long-term health and survival of that retina. The peak time of the 30 Hz flicker ERG response is the most sensitive measure.[29,32-34] The mfERG findings in patients with BCR usually show generalised peak time delay; localised areas of abnormality tend not to occur. Typical ERG findings are shown in Figures 2 and 3, which also demonstrate the ability of the ERG objectively to indicate the efficacy of treatment. It is of interest that a recent report of the use of daclizumab in the treatment of BCR not only detailed ERG improvement in association with clinical improvement, but also described some patients where apparent clinical improvement was associated with deterioration in electrophysiological function.[35] Further study is clearly indicated to assess the full significance of those observations.

OTHER FORMS OF UVEITIS

There is currently a paucity of published data on the ERG changes in other forms of uveitis. It is the experience of this author that, similar to BCR, the predominant change is of peak time delay in the cone system derived 30 Hz flicker ERG, and this delay can occur in the absence of significant amplitude reduction. As in BCR, the degree of ERG abnormality may be much greater than would be predicted by sometimes minor symptoms and/or signs.

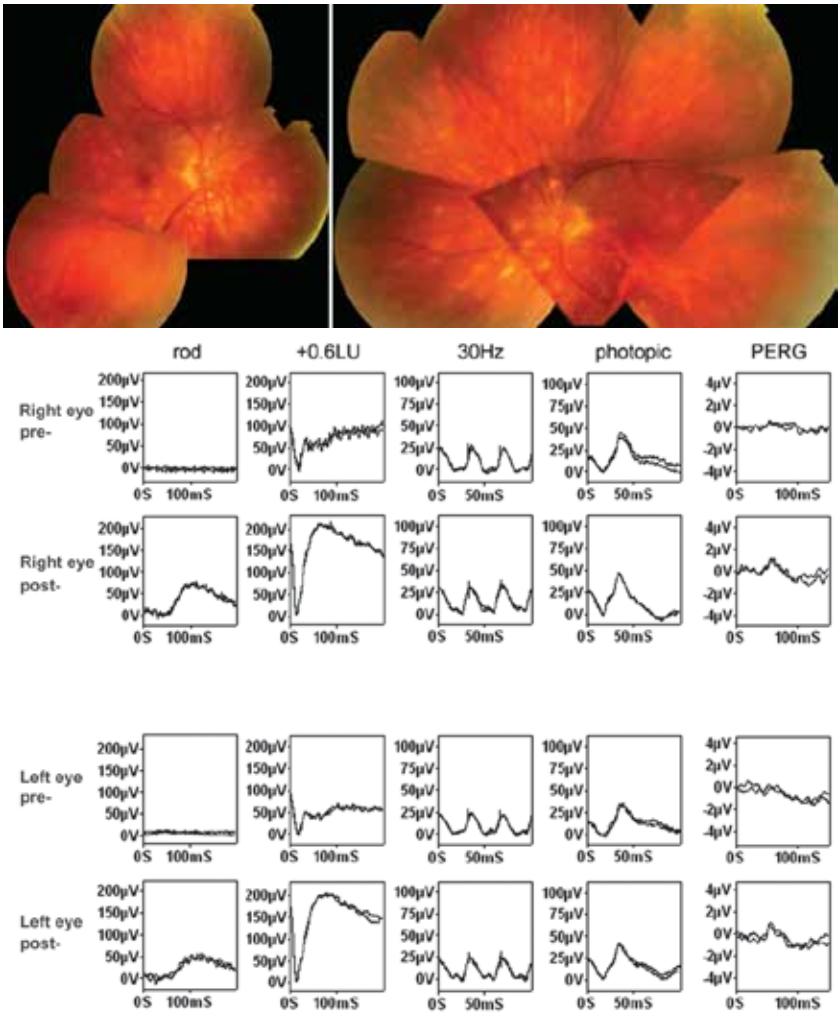


Figure 2: Birdshot Chorioretinopathy. Improvement following 4 months treatment with systemic steroids and cyclosporine. The initial recordings from both right and left eyes have an electronegative waveform. Although both eyes show a mildly subnormal ERG a-wave following treatment, in keeping with some loss of photoreceptor function, there is profound ERG improvement with restoration of a normal waveform and shortening of 30Hz flicker peak time. PERG shows improvement in macular function

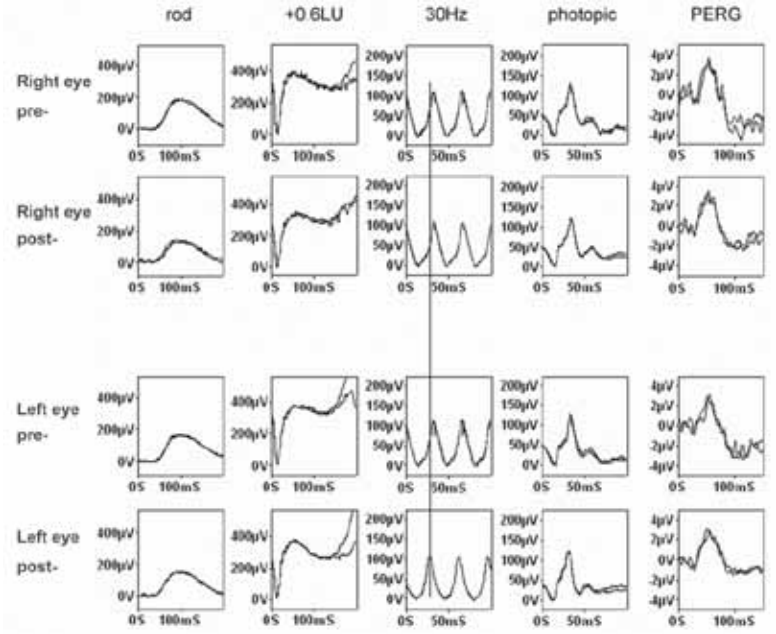
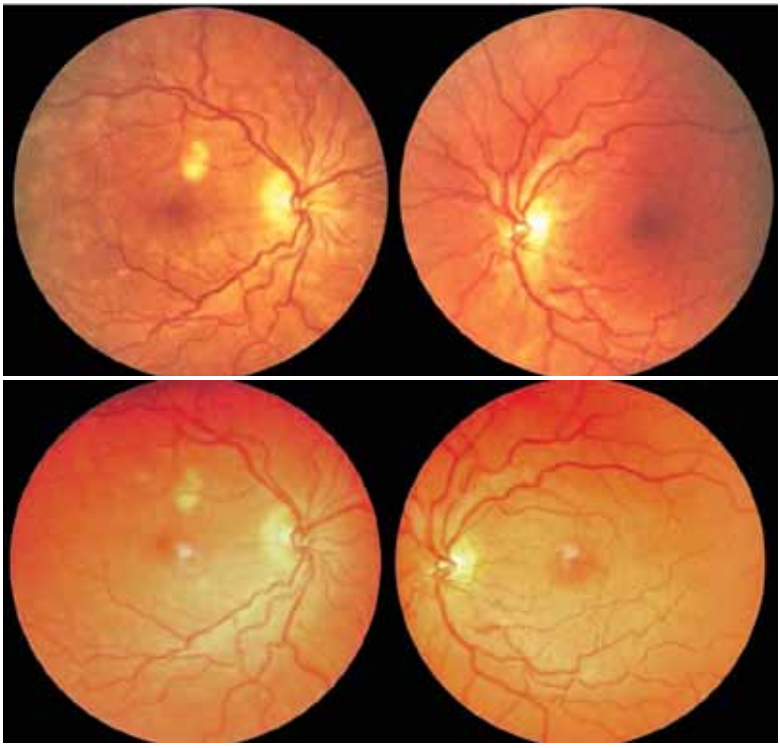


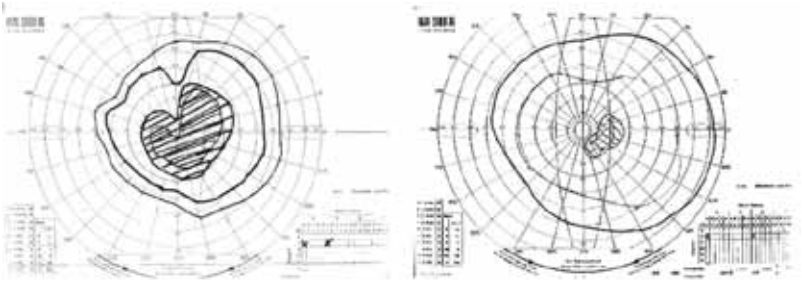
Figure 3: Birdshot chorioretinopathy. Improvement following intravitreal triamcinalone (LE), but not following sub-Tenon's injection (RE). The improvement is seen in 30Hz flicker peak time. Visual acuities in both eyes were 6/9 prior to and following treatment, demonstrating the value of electrophysiology in the objective assessment of treatment efficacy

AZOOR

The exact aetiology of AZOOR (acute zonal occult outer retinopathy) is not fully understood, but it may be consequent upon inflammatory disorders such as multifocal inner choroiditis (MIC), punctuate inner choroidopathy (PIC), multiple evanescent white dot syndrome (MEWDS), acute macular neuroretinitis (AMN), etc. The disorder was first characterised by Gass,[36] who reported 13 patients with rapid visual field loss, usually self-limiting, associated with photopsia but unaccompanied by significant ophthalmoscopic abnormality. The majority of patients were young women, reflecting the predilection of the precipitating disorders.

There is usually progressive visual loss over a period of a few weeks or months, but can also be acute. The patient usually describes positive phenomena in the affected field, which may be obvious photopsias but is often described as "scintillating" or "shimmering". The disorder is usually asymmetrical and may be unilateral; there is variable severity of visual acuity loss. The ophthalmoscopic changes reflect the underlying disorder with choroidal changes or scarring in PIC. In some cases the fundus appearance is normal, and it may be assumed that the precipitating disorder may have been MEWDS as the fundus changes in MEWDS may be minimal in a matter of weeks following onset. In particular, the fundus in





Figures 4: (Continued)

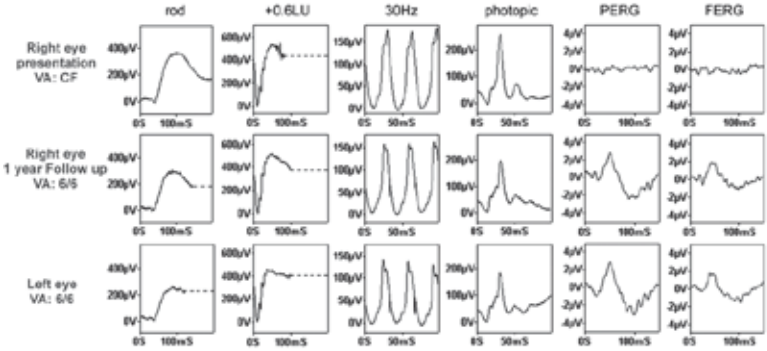
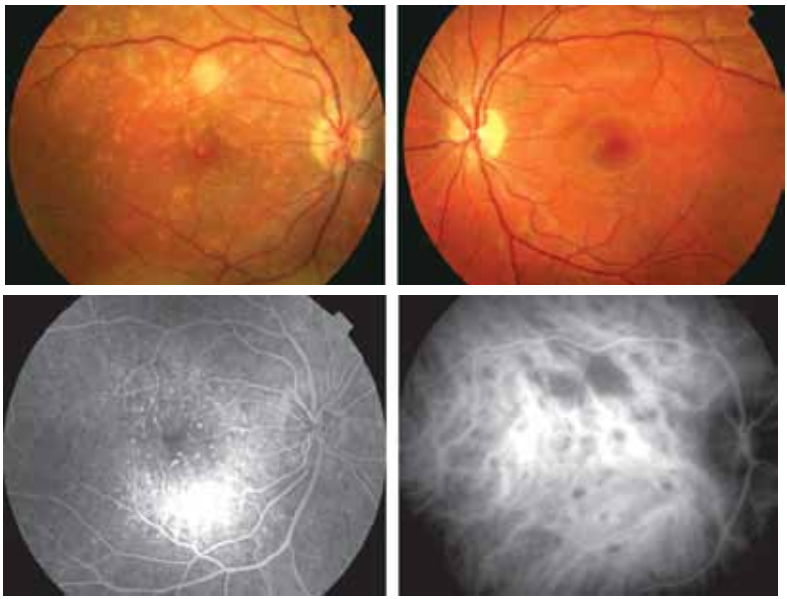


Figure 4: MEWDS. Fields at presentation (RVA CF) show a dense central scotoma, and marked improvement at 6 months (RVA 6/9). Initial recordings show no ERG abnormality but an undetectable pattern of ERG (PERG) and focal ERG (FERG). PERG and FERG are normal after 1 year



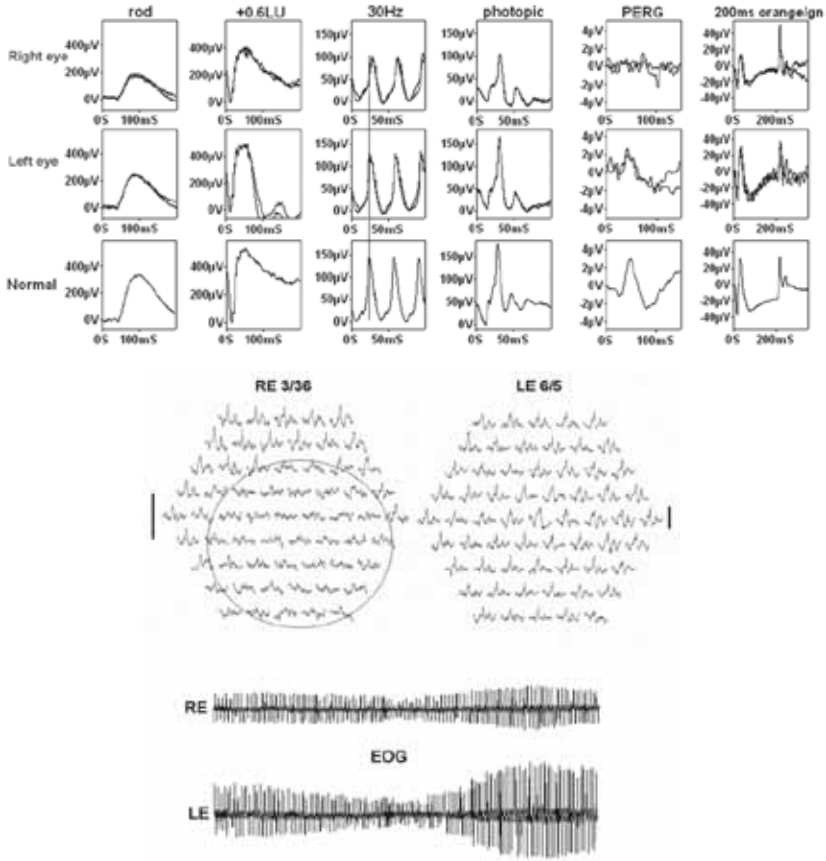


Figure 5: This 32 year old female presented with a sudden onset of central acuity loss and photopsias in the right eye. Fundus appearance, fundus fluorescein angiography and indocyanine green angiography are in keeping with MEWDS. PERG is undetectable I keeping with severe macular dysfunction. However, ERG shows generalised retinal dysfunction in the right eye, as seen in the delayed 30Hz flicker ERG, and EOG light rise (upper trace right eye, lower trace left eye) is markedly reduced, not explained by any reduction in rod ERG and thus suggesting generalised dysfunction at the level of the RPE. The extent of the macular dysfunction is shown in the mfERG, where there is profound central retinal dysfunction not predictable on the basis of the imaging studies

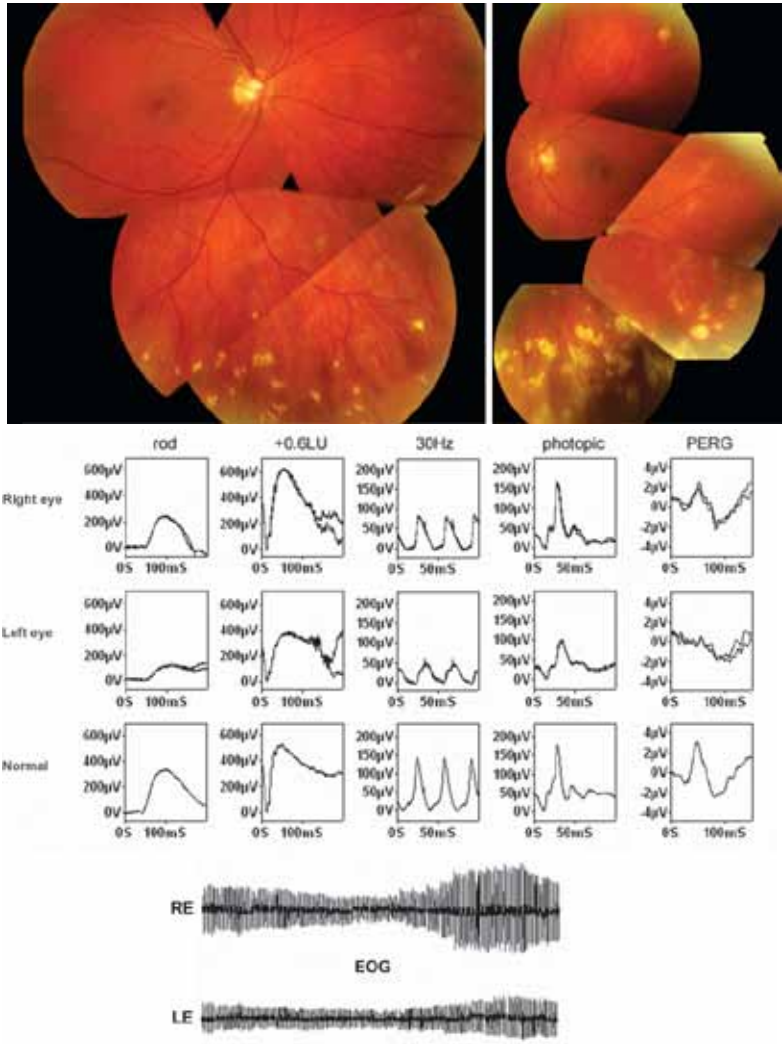


Figure 6: This 47 year old female has MIC in both eyes. The left eye developed photopsias and shows generalised retinal dysfunction with overall ERG amplitude reduction, marked delay in the 30Hz flicker ERG and a reduced EOG light rise in keeping with AZOOR. The right eye findings show no significant electrophysiological abnormality

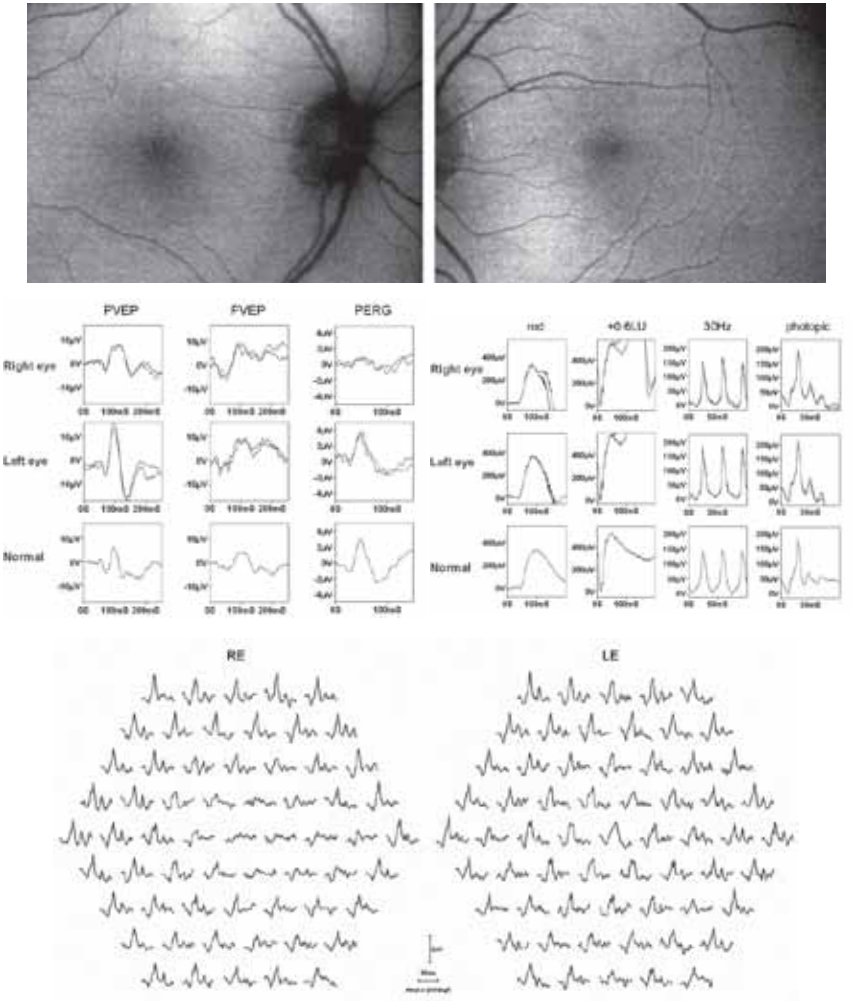


Figure 7: A 33 year old female with one month history of reduction in left visual acuity following Dengue fever. Fundoscopy and fundus autofluorescence imaging were normal (autofluorescence images are shown), and this was therefore originally thought to reflect optic nerve dysfunction. Although the pattern VEP is delayed and reduced from the right eye, the PERG confirmed maculopathy, the spatial extent of which is demonstrated by mfERG. ERGs are normal showing that the dysfunction is confined to the macula. From Holder GE. Electrophysiological assessment of optic nerve disease. *Eye* 2004; 18: 1133–1143 (with permission)

AZOOR has no specific abnormality in the area of retina responsible for the visual field loss. ICG angiography may reveal characteristic changes even when the fundus appearance has returned to normal.

Electrophysiological assessment shows that retinal dysfunction is responsible for the visual field loss.[37-39] The 30 Hz flicker ERG is the most sensitive measure of dysfunction, usually showing marked peak-time delay. The rod system is involved in some patients. Although some localised loss of photoreceptors in relation to a disorder such as PIC or MIC may result in ERG amplitude reduction due to loss of photoreceptor function, this represents localised loss of function and does not explain the generalised dysfunction suggested by the timing shift in the flicker ERG in patients with AZOOR. Pattern ERG abnormalities reflect macular dysfunction, the spatial characteristics of which can be revealed by mfERG. There is a reduced EOG light rise, not explained by the degree of rod photoreceptor loss, and therefore in keeping with generalised dysfunction at the level of the RPE, and thus suggesting RPE involvement to be intrinsic to the disorder. Currently, it is not understood why patients with MIC, PIC, MEWDS, POHS, etc. are at risk of developing the generalised dysfunction associated with AZOOR. An autoimmune mechanism is one possibility. It is also possible that antiretinal antibodies may have been induced by release of retinal antigens, possibly related to an infective agent, but Jacobsen et al[37] found no evidence to support this.

The findings from a patient with MEWDS appear in Figure 4. There was no evidence of generalised retinal dysfunction at presentation (3 days). There was complete recovery and normalisation of function within one year. It has previously been demonstrated that the onset of MEWDS can trigger AZOOR in some patients as in Figure 5. Normalisation of function is not usually associated with AZOOR.

Other Inflammatory Disease

There are minimal published data on the electrophysiology of other inflammatory disease. The disorders referred to above as implicated in the pathogenesis of AZOOR may be associated with electrophysiological abnormalities, but these are non-specific. Those diseases which cause localised loss of retinal function, such as MIC or PIC, may show amplitude reduction in the bright flash ERG a-wave, in keeping with some loss of photoreceptor function, but severe generalised retinal dysfunction, as particularly characterised by an increased peak-time in the 30 Hz cone flicker ERG, does not occur unless there has been the development of AZOOR. This can be seen in Figure 6, where both eyes have evidence of previous choroiditis but it is only the eye with positive phenomena in the form of photopsias where there is generalised retinal dysfunction as indicated by the delayed and reduced ERGs. Those disorders that present with central retinal dysfunction, such as macular neuroretinitis, will have abnormalities in multifocal or pattern ERG, but full-field ERGs are usually unaffected. It should be recalled that macular dysfunction need not be accompanied by an abnormal macular appearance. Figure 7 illustrates a patient with presumed inflammatory maculopathy consequent upon dengue fever, initially thought to be an inflammatory optic neuropathy, and also demonstrates the value of pattern and mfERG in differentiating between macular and optic nerve dysfunction.[40] One report has appeared detaining the electrophysiological findings in a case of acute syphilitic posterior placoid chorioretinitis.[41] Although visual fields, ERGs and mfERGs were initially abnormal, all parameters normalised following successful treatment.

CONCLUDING REMARKS

In conclusion, although the objective assessment of retinal function with electrophysiology may enable improved management of some inflammatory disorders, there are relatively few published data. It is anticipated, particularly as increasing numbers of agents delivered by intra-vitreal injection become available, that the role of ERG will increase; not only in the evaluation of efficacy in the treatment of the primary disorder, but also in the exclusion/evaluation of potential retinal toxicity.

KEY POINTS

- Electrophysiology provides objective assessment of visual pathway function
- Electrophysiology facilitates diagnosis by enabling the distinction between localised and generalised retinal dysfunction, and between optic nerve and macular dysfunction

- The severity of dysfunction is best revealed by electrophysiology; symptoms and signs can be poor indicators
- Electrophysiology provides objective monitoring of the efficacy of treatment, enabling management decisions to be taken with increased confidence, and can assist in the initiation of treatment
- Improved retinal function following treatment is presumed to be beneficial to long-term retinal health; ERG monitoring is therefore likely to result in improved prognosis

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Prof. Graham E. Holder
Consultant Electrophysiologist
Director of Electrophysiology
Moorfields Eye Hospital
London EC1V 2PD, UK

Honorary Professor
Institute of Ophthalmology
University College London

Molecular techniques as diagnostic methods

Uwe Pleyer, Germany

3

The underlying cause of intraocular inflammation is often difficult to establish. However, in particular an infectious origin or masquerade syndrome will benefit from subsequent and specific therapy. Some of the most common causes of uveitis e.g. herpes keratouveitis and toxoplasmic retinochoroiditis are not accessible using blood testing because of the high rate of seropositive individuals in the healthy population. Investigations using molecular biological techniques and antibody testing, i.e. the analysis of specific antibody formation within the eye have been shown to provide useful information. In addition, several new aspects for infectious causes in uveitis have been revealed e.g. in Posner Schlossman syndrome and CMV anterior uveitis.

Molecular techniques as diagnostic methods

U. Pleyer
Charité, Berlin

uwe.pleyer@charite.de

Why

How

Results

Future

Intraocular infections

Differential diagnosis

APMPPE – ARN – Amöbiasis – Borreliosis – Behcets Disease – Brucellose – Birdshot Retinopathy – Endogenous Endophthalmitis – Echinococcosis – Candidiasis – Colitis ulcerosa -Fuchs'sche Heterochromic Cyclitis – Frosted Branch Angiitis – Gonorrhö – Giardiasis – HLA B27+ Uveitis anterior – Herpes simplex Uveitis – Histoplasmosis – Kryptococcosis – Lepra – Leptospirosis – Lymphoma – Wegener Gr. – Morbus Bechterew – Morbus Reiter – Morbus Whipple – Morbus Eales – Kawasaki – Morbus Crohn – Onchocerccosis – Psoriasis – Posner Schlossman Syndrome – relapsing Polychondritis – Serpingeous Chorioiditis – Sympathetic Ophthalmia – Toxoplasmosa Retinochorioiditis – Tuberculosis - Takayasu Arteritis – Toxocara – Vogt Koyanagi Harada Syndrome – Varicella Zoster Uveitis - Zystizercosis

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Why

How

Results

Future

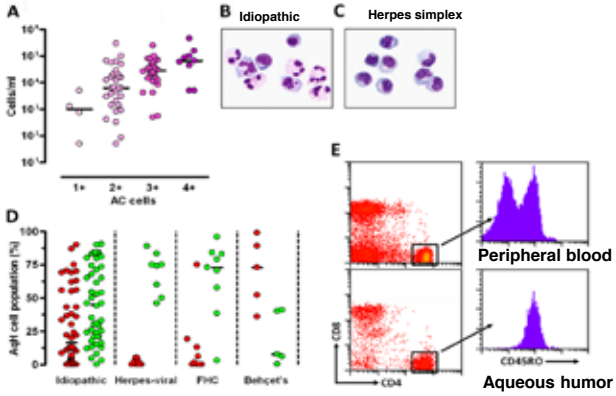
Aqueous humour analysis

Procedures

Microscopy
PCR
Antibody synthesis (ELISA)
Western blot
Micro array

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Aqueous humour analysis



Red	Granulocytes
Green	Lymphocytes

Alastair K.O. Denniston and S. John Curnow, In:
Pleyer U, Forrester J: Essentials in Ophthalmology, Springer 2008

Aqueous humour analysis: PCR

Why

How

Results

Future

Procedures
Microscopy
PCR
Antibody synthesis
(ELISA)
Western blot
Micro array

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Why

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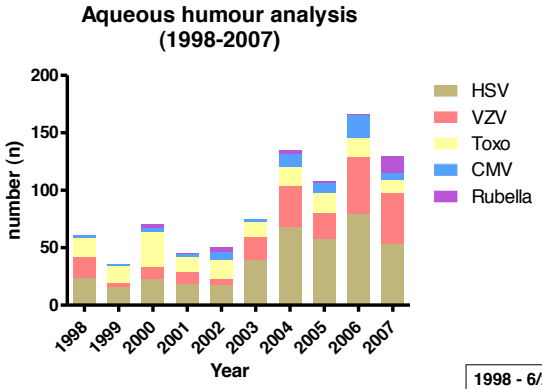
Future

Aqueous humour analysis: Charité



1998 - 6/2008
n= 1363

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Aqueous humour analysis: Charité

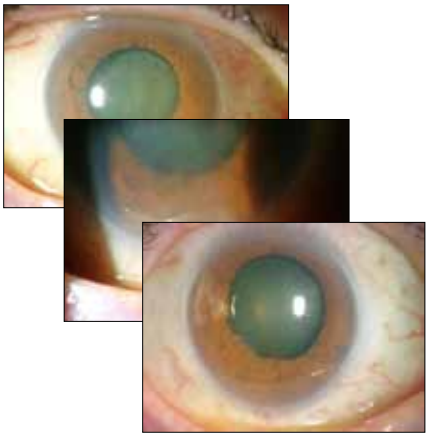
Anterior Uveitis

Intermediate Uveitis

Posterior Uveitis

Uveitis anterior

- Recurrent anterior uveitis
  Fibrin exsudation
  Nonresponsive to topical
  Prednisolone for 3 weeks
- Aqueous humour analysis:
  local VZV-AB synthesis ++
  (PCR +)
- DX: „Zoster sine herpete“
- Valacyclovir 2000 mg/d
- Intracameral Triamcinolone
  (o.o5 ml - 2 mg)
- VA 20/100 - 20/20



Aqueous humour analysis: Charité

Why

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Future

Herpes Virus associated (kerato) uveitis

Specificity and sensitivity > 93%
Significant correlation Dx/aqueous analysis
($p<0.01$, Cohen‘s Kappa)

Change in initial treatment

43/398 patients (10.8%)
- positive: 34 patients
- negative: 9 patients

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Why

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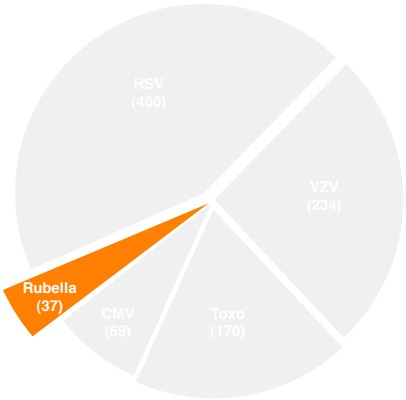
Future

Aqueous humour analysis: Charité



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Why

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Future

Fuchs' Uveitis Syndrome (FUS)

37 FHC patients with typical clinical findings
15 Controls (7 HSV Keratouveitis, 5 granulomatous iridocyclitis, 3 Posner-Schlossman-syndrome)

Paired aqueous humor/serum analysis
IgG-antibody production against

Rubella V, HSV, VZV, CMV, Toxoplasma gondii

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Why

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Future

Fuchs' Uveitis Syndrome (FUS)

	FUS	Control
Persons	63	46
Male	34 (54.0%)	23 (50%)
Female	29 (46.0%)	23 (50%)
Age	46.9 ± 13.8 years	50.3 ± 18.0 years
Seropositive, RV	58 (100%)	42 (91.3%)
Intraocular antibody synthesis against RV	58 (100%)	0 (0%)

Ruokonen PC et al.
Graefes Arch Clin Exp Ophthalmol. 2010;248:565-71.

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Why

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Results

Future

Fuchs' Uveitis Syndrome

RV vaccination	FHC	Control
Yes	1 (1.6%)	3 (6.5%)
Not known	1 (1.6%)	4 (8.7%)
No	61 (96.8%)	39 (84.8%)

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

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Future

Fuchs' Uveitis Syndrome

- 63/63 FHC patients: intraocular Rubella virus antibody
- 0/46 control patients: intraocular Rubella virus antibody
- 11/63 Rubella positiv FHC patients
  intraocular antibody synthesis against other viral antigens
  (8x HSV, 1x VZV, 2CMV)

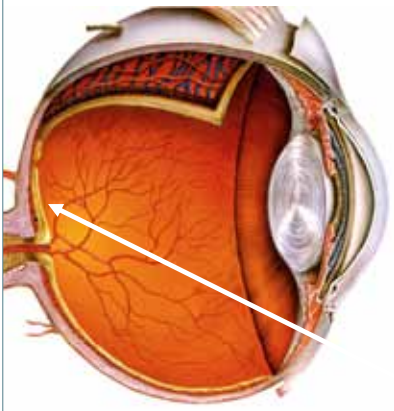
Conclusions

- FHC: strongly associated with intraocular Rubella virus antibody
- Coincidence, cross reactions or false positive results ?

Ruokonen PC et al.
Graefes Arch Clin Exp Ophthalmol. 2010;248:565-71.

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Aqueous humour analysis: Charité



Anterior Uveitis

Intermediate Uveitis

Posterior Uveitis

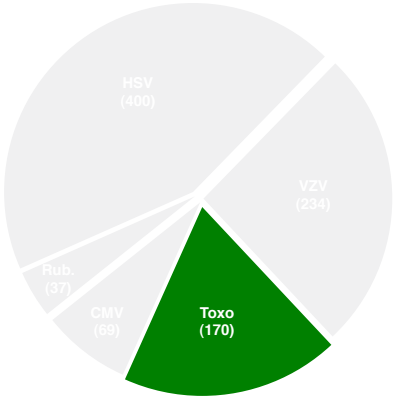
Why

How

Results

Future

Aqueous humour analysis: Charité



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Aqueous humour analysis: Charité

2000 - 2007

Toxoplasma gondii retinochoroiditis

170 aqueous humour samples

- **Age 9 – 78 years**
- **Male : Female = 1 : 1.3**

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Why

How

Results

Future

Aqueous humour analysis: Charité

Ocular toxoplasmosis

Specificity and sensitivity > 95%
Significant correlation Dx/aqueous analysis (p<0.01, Cohen's Kappa)

Liekfeld et al., Graefe's Arch Clin Exp Ophthalmol: 2000; 238:222-227

Change in initial treatment

23/170 patients (13.5%)
- positive: 14 patients
- negative: 9 patients

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Why

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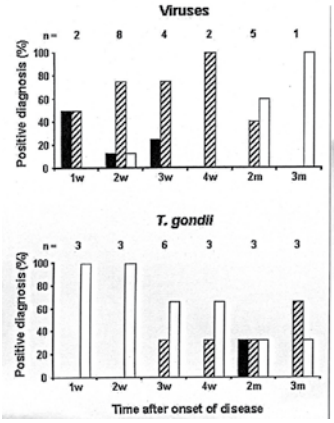
Aqueous humour analysis: „Timing“



PCR

ELISA

ELISA + PCR

DeGroot-Mijnes et al., AJO; 2006; 141: 313-318

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Why

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Aqueous humour analysis: Charité

APMPPE: Characteristics

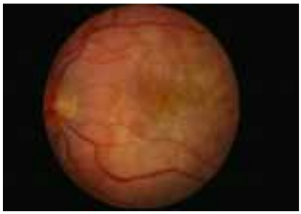
Typical multiple, flat, round and circumscribed yellow white lesions at the level of RPE scatered behind the equator

Self resolution leaving fields of depigmentation and pigment clumping

Good visual prognosis

Unknown etiology...

(Para)infectious ?



CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Why

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Aqueous humour analysis: APMPPE

Serum evaluation: No signs of an acute viral infection

4/6 patients (67%) local anti-viral antibody synthesis

- **2 patients anti - CMV**
- **1 patient anti - VZV**
- **1 patient anti - HSV**

0/11 control samples anti-viral antibody synthesis
Possible role of viruses in the onset of APMPPE

Brezin et al., APMPPE after hepatitis B vaccine.
Arch Ophthalmol. 1995 Mar;113(3):297-300.
Azar et al., APMPPE associated with an adenovirus type 5 infection.
Am J Ophthalmol. 1975 Dec;80(6):1003-5

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Why

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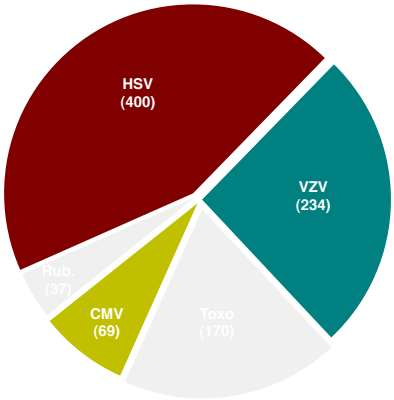
Future

Aqueous humour analysis: Charité



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Results

Future

Acute Retinal Necrosis Syndrome: Definition *

- 1971 - first reported by Urayama, Japan
- Acute onset of Panuveitis
- In 1/3 bilateral course
- Peripheral progressive retinal necrosis
- Occlusive vasculitis
- Diffuse anterior and vitreal inflammation

- 1981 – evidence of viral etiology Culbertson

*Criteria of American Society of Uveitis 1994

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

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Aqueous humour analysis: ARN

Patients from 1994 -2008

- 24 eyes of 18 patients (f:m= 8:10)
- Age 16 to 73 years
- Follow up: 12 - 132 (m=36) months
- HIV ass. CMV retinitis/ PORN excluded

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Why

How

Results

Future

Aqueous humour analysis: ARN

Results: Aqueous Analysis

- Viral origin confirmed in 18/18 patients
- Detection of intraocular Viruses

	Antibody	PCR
VZV	(10 x)	(4/5)
HSV Type I	(4 x)	(3/4)
CMV	(3 x)	(3/3)

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Why

How

Results

Future

Primary intraocular lymphoma: differential diagnosis

Sen HN, Bodaghi B, Hoang PL, Nussenblatt R
Ocul Immunol Inflamm. 2009; 17: 133–141

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

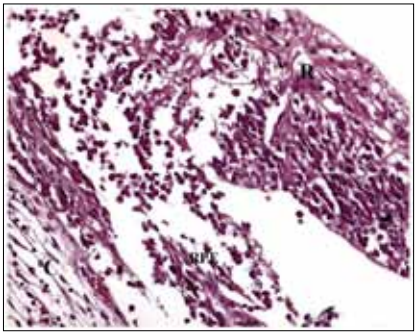
Why

How

Results

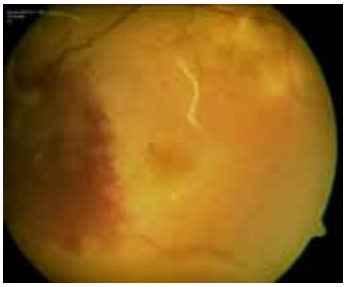
Future

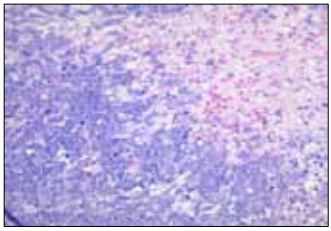
Primary intraocular lymphoma: differential diagnosis



CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Primary intraocular lymphoma: differential diagnosis





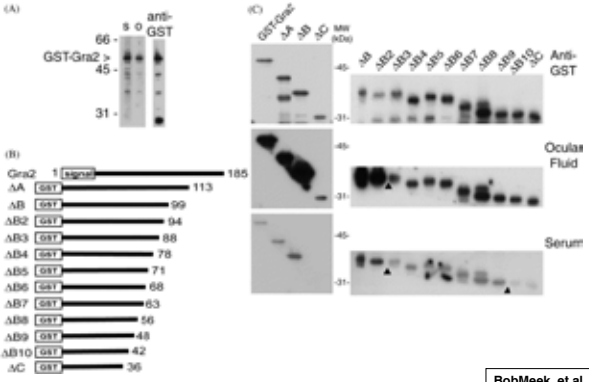
Aqueous humour analysis: Future

Why

How

Results

Future



BobMeek, et al., Prog Ret Eye Res 22: 2003, 391-415

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DOG 2008

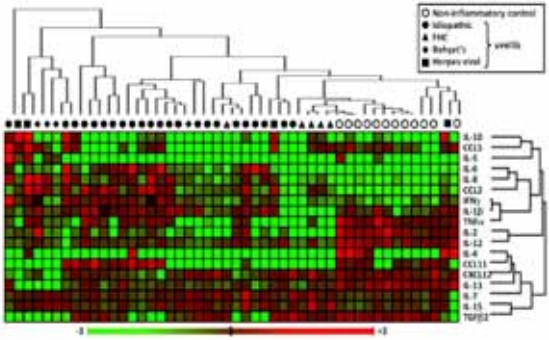
Why

How

Results

Future

Aqueous humour analysis: Future



Alastair K.O. Denniston and S. John Curnow, In:
Pleyer U, Forrester J: Essentials in Ophthalmology, Springer 2008

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Why

How

Results

Future

Aqueous humour analysis: Summary

- AqH can identify/confirm specific pathogens
- Provides diagnostic information that will affect subsequent treatment
- Analysis of pathogen-specific antibodies is an effective method to identifie viral, (bacterial) and parasitic pathogens
- New methods may allow the full sequencing of all non-human RNA/DNA in the AqH sample, allowing identification of rare and novel pathogens

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Prof. Uwe PLEYER
Charité, Berlin
uwe.pleyer@charite.de

Notes

Imaging in uveitis

Carl P. Herbort, Switzerland

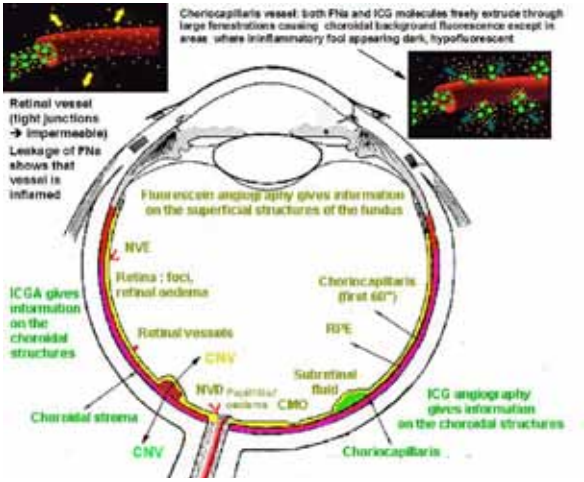
4

1. Fundus photography and fluorescein angiography (FA)

Fundus examination, fundus drawing and photography is at our disposal since ophthalmoscopy allowed to analyse the ocular fundus and documents the apparent aspect of inflammatory fundus lesions but it does not allow to go beyond or to give the dynamic aspects of a lesion process.

Since the late sixties, fluorescein angiography (FA) allowed to give a dynamic aspect of superficial structures of the inflammatory lesions of the fundus. The gain achieved by FA for superficial fundus lesions is significant as it gives more information on the pathological structures, in particular on the activity or the extension of inflammatory lesions such as papillitis, retinal neovessels on the disc or elsewhere, subretinal fluid/exudative retinal detachments or areas of atrophy. Its most useful information however is on retinal vessels. It shows inflammation of capillaries and veins such as in birdshot chorioretinitis. It precisely shows the extent of vasculitis especially of veins particularly in Behçet's uveitis, intermediate uveitis, tuberculous chorioretinitis or posterior ocular sarcoidosis to name only a few of the conditions that cause retinal vasculitis. It also precisely delineates vascular non perfusion and ischaemic areas. Another structure that is advantageously investigated by FA is the pigment epithelium (PE) where defects (window effect) or clumping of pigment (masking effect) are well shown by FA. Except for lesions of the PE and for vasculitis that is sometimes not clearly visible on fundus examination, it mostly does not detect new fundus lesions not seen on fundus examination but enhances information on lesions detected by fundus examination or fundus photography.

Because of the physical characteristics of the fluorescein molecule (fluorescence in the visible wavelengths), this technique does however not allow to analyse structures beyond the pigment epithelium except for the choriocapillaris in the early phase (±50-60 sec.) of the angiographic sequence. For all inflammatory lesions situated beyond the PE, indocyanine green angiography is needed.



2. Exploration and understanding of choroidal inflammation : indocyanine green angiography (ICGA)

The choroid is at least as often if not more often the site of intraocular inflammation as the retina. Because choroidal structures were not accessible to sensitive and performing investigational procedures, analysis of inflammatory events in these structures lagged behind. This was at the origin of the inadequate appraisal of choroidal inflammation and the use of imprecise or vague terminologies such as “White Dot Syndromes”. Thanks to indocyanine green angiography (ICGA), access through the retinal pigment epithelium (RPE), to the choroidal compartment has been granted to the clinician. Therefore, more precise information on inflammatory mechanisms has allowed to establish on one hand a classification based on disease behaviour and on the other hand direct monitoring of disease evolution in the choroid has been made possible.
With the help of ICGA it has been established that in the choroid at least two main inflammatory patterns touching 2 different choroidal structures are occurring. Firstly, inflammation of the choriocapillaris causing partial or complete non perfusion is very well recognised by its typical ICGA features consisting of confluent and/or georaphic zones of hypofluorescence and constitutes a group of diseases that are called inflammatory choriocapillaropathies (PICCP, primary inflammatory choriocapillaropathies), including such entities as Multiple Evanescent White Dot Syndrome (MEWDS), Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE) or multifocal choroiditis.
On the other hand, there is a totally different category of choroiditis, where the inflammation is principally occurring in the choroidal stroma, which is the site of mostly granulomatous infiltration and is called stromal choroiditis. When the target of the inflammatory reaction is specifically in the choroid such as in Vogt-Koyanagi-Harada disease (VKH) or Sympathetic Ophthalmia (SO) we speak of primary stromal choroiditis and when the choroids is just the structure where a systemic disease elects to manifest itself such as sarcoidosis we speak of secondary stromal choroiditis,
Beside the fact that ICGA has helped us to classify choroiditis on the base of disease mechanism, In most of these cases, proper monitoring of disease activity reaching a satisfactorily grade of accuracy is only available by ICGA..

3. Optical Coherence Tomography (OCT) in Inflammatory and Retinal Diseases.

Optical Coherence Tomography (OCT) has gradually invited itself into everyday practice. The imaging quality is steadily improving with new generations of instruments giving fascinating insight into the retina. Although OCT investigation gives stunning pictures of the retina it is basically imaging those structures for which imaging access was already possible. The novelty is, with the new machines especially, the degree of precision of the information we can gather: A corollary to this first point, is the fact that we can get this information instantly without invasive procedures. For conditions such as choroïdal neovessels, much closer follow-up has allowed, in parallel with the availability of potent intravitreal anti-VEGF therapy to improve drastically the management of AMD cases. In inflammatory diseases the availability of OCT has changed our attitude in the management of CME, increasingly based on OCT profile rather than strictly functional parameters. In diabetic maculopathy also OCT came along with the advent of new performing therapies the effect of which can so be optimally verified. The drawbacks of OCT is the fact that information is lost or OCT is impossible in turbid media and that the information on the underlying choroid is limited. Inflammatory cases will be presented showing that OCT changed our way to manage inflammatory cases where the macula is involved. At the present point of the technology, OCT is however not giving any help in choroidal inflammation unless choroiditis produces lesions in the neighbouring structures such as the retina. It then is useful to follow this spill-over inflammation but not the primay inflammation that can only be followed by appropriate methods for the choroid such as indocyanine green angiography. More performing OCT machines are now able to give information on the choriocapillaris and is becoming useful in inflammatory disease of the choriocapillaris.

4. Ultrasound biomicroscopy (UBM) in ocular inflammatory diseases.

Evaluation of the inflammatory involvement of the iris stroma and retroiridal face, ciliary body, pars plana and retroiridal vitreous is sometimes important. These structures are not readily accessible with routine examination methods. Evaluation of the retrolenticular and retroiridal space is even more important when no visual access to the posterior segment is possible because of opaque media. In such cases ultrasonography is the method of choice. B-scan ultrasonography has become an essential and well-established device to help diagnose and manage ocular and orbital disorders. More recently high-frequency ultrasonography has been introduced and made available to clinical practice. The method has been named ultrasound biomicroscopy (UBM) and is based on high-frequency transducers incorporated into a B-mode clinical scanner. This technology allows quasi-histological sections up to 3-6 mm in depth to be obtained in vivo,

giving access to structures in the anterior part of the posterior segment that cannot be visualised otherwise or that are inaccessible because of opaque media. The method has been shown to be valuable in inflammatory pathologies of the anterior part of the ciliary body and retroiridal space.

5. Fundus autofluorescence (FAF) in uveitis

Autofluorescence has become one of the centers of interest in fundus imaging since the confocal scanning laser optthalmoscope (cSLO) allows to detect low intensity (auto)fluorescence such as lipofuscin levels in the retinal pigment epithelial cells. This imaging technique in the field of inflammatory diseases is especially useful for the group of diseases that affect the external retina and/or the retinal pigment epithelium (RPE) such as the inflammatory diseases of the choriocapillaris including Multiple Evanescent White Dot Syndrome (MEWDS), Multifocal Choroiditis (MFC) or Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE).
The only system that presently allows to routinely obtain autofluorescence images is the Heidelberg retina angiograph (HRA). Autofluorescence images can be obtained in the short wave mode (488nm) or in the near-infrared mode (787 nm). Fundus autofluorescence obtained with the cSLO in the short-wave mode monitors basically the content of lipofuscin in the RPE. The near-infrared auto-fluorescence mode reveals melanin contaning cells such as RPE-filled cells in the fovea. Other structures or pathological conditions such as drusen and basal membrane deposits are also detected using cSLO auto-fluorescence short-wave mode.
Fundus autofluorescence (FAF) is principally produced by the lipofuscin present in the RPE cell.
This material is originating from the photoreceptor outer segments and its degradation process or accumulation in the RPE cell lysosomes seems to be an indicator on the quality of the RPE cell metabolism. In inflammatory diseases of the fundus, FAF analysis can contribute additional information to other imaging methods to study the lesion process.
The inflammatory diseases that produce patterns of increased or decreased auto-fluorescence are mainly those entities whose inflammatory process involves the choriocapillaris-RPE complex and the outer retina comprising most of the primary and secondary inflammatory choriocapillaropathies.
The information we have so far is scarce and difficult to understand, still awaiting standard interpretation rules. The FAF pattern may be different in the same disease entity and probably depends on the severity and the stage of the disease. It is not sure whether autofluorescence changes are due to direct RPE dammage, which seems probable, or indirect dammage coming from damaged outer retina or both. In the group of the different diseases of the choriocapillaris, FAF is more pronounced on the more benign side of the spectrum such as in MEWDS and similar choriocapillaropathies or in entities with smaller chorioretinal lesions such as in MFC.
On the other side, in conditions with more widespread zones of involvement such as in APMPPE and serpiginous choroiditis, FAF is very often decreased within the active lesions being sometimes visible on the border of active or progressing lesions. In these conditions bright FAF is often present in the center scarred lesions, but this type of autofluorescnce is not reflecting RPE dysfunction but accumulation of cellular fluorophore debris.

Fundus autofluorescence might become a useful complementary imaging method in addition to fundus examination and photography, fluorescein angiography and indocyanine green angiography useful for the investigation of inflammatory choriocapillaris diseases: It might also bring additional information on the lesion mechanism involved in this spectrum of inflammatory diseases.

6. Laser flare photometry (LFP) for uveitis.

Although laser flare photometry (LFP) is imaging in vivo the cloudy streak produced by back-scattered light from anterior chamber proteins in inflammatory states (Tyndall effect), it is not really an imaging method as no photoshots are taken but the backscattered light is quantitatively analysed. As it completes investigational methods for intraocular inflammation it is probably justified to include it here.
The laser flare photometer comprises a laser light beam (Helium-Neon or diode laser) of constant power (25microW) and a diameter of 20 micrometers that is directed into the anterior chamber at an angle of 45^{o} to the antero-posterior axis. At an angle of 90^{o} degrees to the incoming laser beam (45^{o} to the antero-posterior axis) a photomultiplyer-photodector unit is placed that detects back-scattered light from the incoming beam through a rectangle window measuring 0.3 X 0.5 mm. **(Figure LFP-1 & 2)**

Figure LFP-1. Schematic diagram of measurement principle in laser flare photometry. The incoming light is in phase as it is produced by a laser beam. Instead of the human eye as the detector of back-scattered light the system contains a photodetector and a photomultiplyer to exactly quantify the amount of photons that are back-scattered which are proportional to the amount of proteins which in turn are proportional the amount inflammation

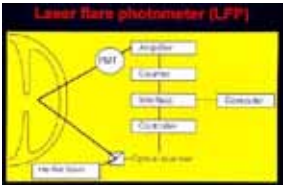
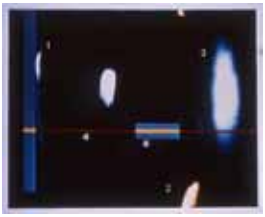


Figure LFP-2. Laser flare photometry : observer's view during measurement procedure. The measuring window has to be placed in the darkest part of the anterior chamber at equal distance from the cornea and the cristalline lens anterior-posteriorily and between the middle and inferior third along the vertical axis. During the measurement sequence, the beam moves up and down from above the window, going through the measurement window and beyond. The photoncount above and below the window will acount for the background light which will be deduced fom the light signal coming from inside the measuring window. Usually seven measurements are taken discarding the lowest and highest values and the five remaining measurements are averaged.



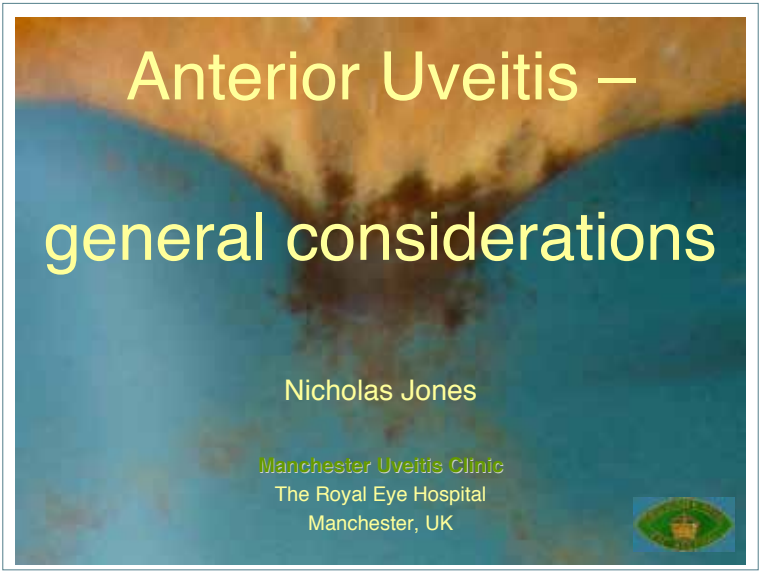
The instrument measures back-scattred light from small molecules such as proteins and this is called laser flare photometry. The measurement units of back scattered light from small molecules are ***number of photons per miliseconds (ph/ms)***. The amount of back-scattered light is proportional to the concentration and size of proteins in the aqueous humor and is so indicating the level of inflammation.

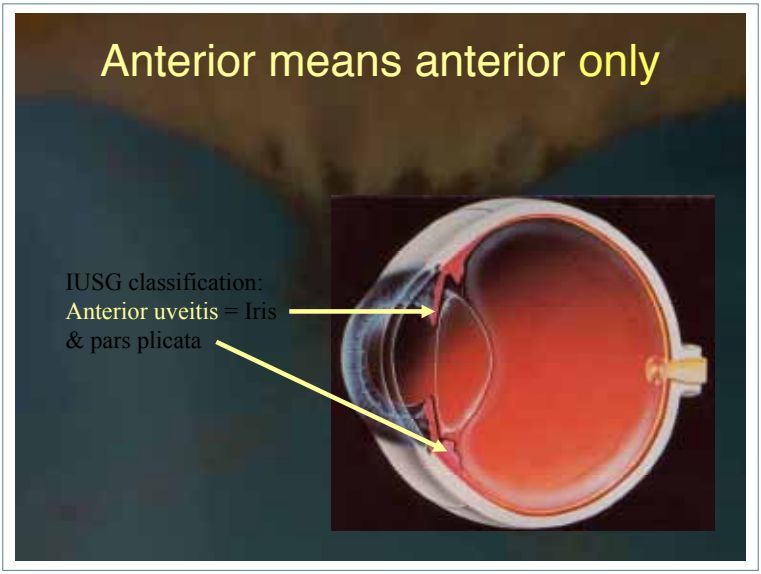
Despite efforts during the last 50 years to standardize and grade anterior chamber inflammation or associated anterior inflammation reflecting posterior inflammatory disease, its evaluation remained very rough and subjective because the use of the human eye through slit-lamp examination is a subjective method with large intra-observer and inter-observer variations. Any “new” or “pseudo-new” nomenclature to better grade anterior inflammation as was recently attempted by the SUN workshop, is doomed to perform equally bad for the reasons cited above. On the other hand laser flare photometry represents the first non-invasive, objective and quantitative method to assess intraocular inflammation. Accumulated evidence so far indicates that LFP has to be considered the standard method to measure intra-ocular inflammation in most cases of uveitis from now on.
In many uveitis centres, LFP together with autorefraction, visual acuity determination and tonometry is part of the routine procedures performed upon reception of the patient. Because LFP is easy to perform with a short learning curve, it is mostly done by paramedical staff. Such routine flare measurements are however far from being the rule in uveitis centres at large. Laser flare photometry is to uveitis what tonometry is to glaucoma practice and it is unthinkable to follow gaucoma patients without including tonometry routinely at each consultation. As for glaucoma, LFP will only be one of the parameters considered to determine the evolution of the disease and its response to therapy but an unavoidable one.
The reason why such an obviously useful tool for the evaluation and management of uveitis has difficulties to be accepted at large in specialized uveitis practice is hard to understand. The fact that the instrument is rather expensive is a possible but not sufficient explanation, as the instrument is now increasingly used in hospitals and centers of countries with less available resources devoted to health care. The fact that the instrument was manufactured in a country that has not immediate access to influencial and largely diffused medical journals might be one part of the explanation. On the reverse the fact that countries that strongly determine medical practice worldwide because they have influence through well difused medical journals

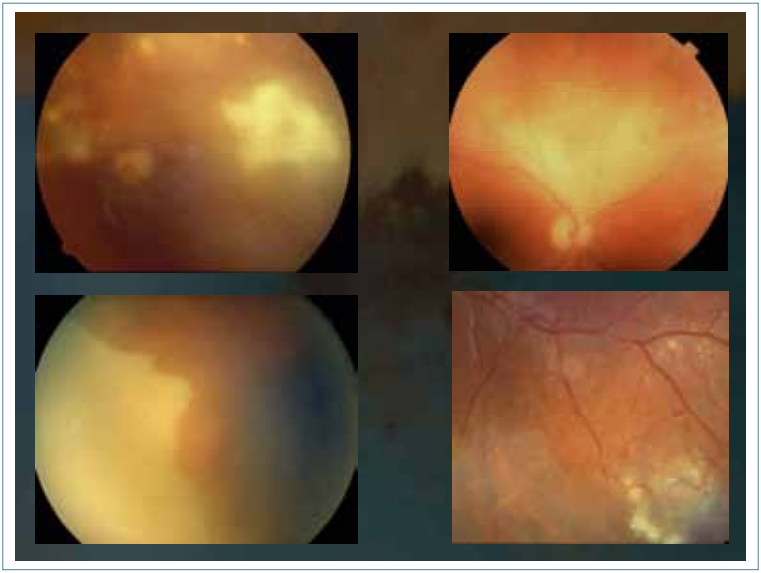
were not at the origin of this technology especially when such investigations are not reimbursed by their health care systems may be another part of the explanation.
At longlast this technology is however going to be part of the standard equipment of uveitis centres.
Hopefully the new instruments with a larger window to record anterior chamber particles will also become the standard measurement mode for aqueous inflammatory cells.

Carl P. Herbort, MD, PD fMER, FEBO
Centre for Ophthalmic Specialised Care (COS, Lausanne, Switzerland) &
University of Lausanne (Lausanne, Switzerland)
carl.herb@bluewin.ch

Notes


Anterior Uveitis –
general considerations
Nicholas Jones
Manchester Uveitis Clinic
The Royal Eye Hospital
Manchester, UK


Anterior means anterior only
IUSG classification:
Anterior uveitis = Iris
& pars plicata

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PASSPORT CHECK

AU Presentations: A diagnostic approach

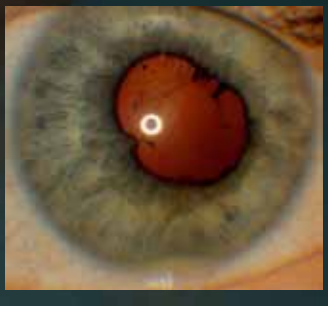
- 1. Acute unilateral non-granulomatous AU
  - (60-70% of all new patients)
- 2. Bilateral or granulomatous AU
  - (10-20%)
- 3. Subacute or chronic AU with unusual features
  - (10%)

Acute unilateral non-granulomatous AU – investigate ?

- History
  - Known medical diagnosis, treatment
  - Ask: arthropathy, bowel, chest, skin, STD, recent illness, travel
- Signs of HLA-B27 positivity (Rothova):
  - Unilateral acute anterior uveitis
  - Age <40 at first attack
  - Recurrent attack
  - Fibrin or cells +++, NO mutton-fat KP
  - Associated AS or Reiter's syndrome
- Investigations: HLA-B27 only (if necessary)

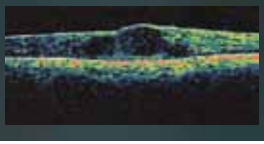
Typical HLA-B27 related AAU

- Unilateral, photophobia, ciliary congestion
- Posterior synechiae, low IOP, exudate



Severe HLA-B27 related AAU

- Plasmoid AC, fibrin web
- Iris haemorrhage
- Macular oedema
- Slow response



Unusually severe, hyperacute HLA-B27 related iridocyclitis

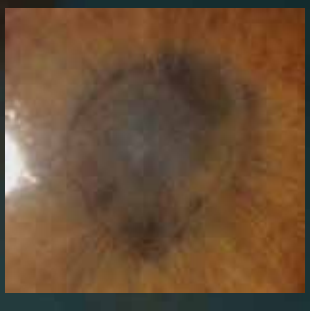
- Very poor visual acuity (<6/60)
- Severe vitritis with plastic anterior uveitis
- IOP 0-5mmHg
- Aqueous tap for micro-organisms
- Very slow response to treatment
- Frequent relapses – cataract, pre-phthisis
- Oral steroid – oral immunosuppression

HLA-B27 related AAU - Lost treatment skills

- Duke-Elder (1966):
- "each attack leaves its mark, producing irreversible changes, and the end-result is indistinguishable from an acute attack of destructive severity which terminates in phthisis."
- "Prompt *treatment* is therefore the vital factor in the prognosis – rest, full atropinisation at the earliest possible moment, local and, if necessary systemic steroid therapy.."

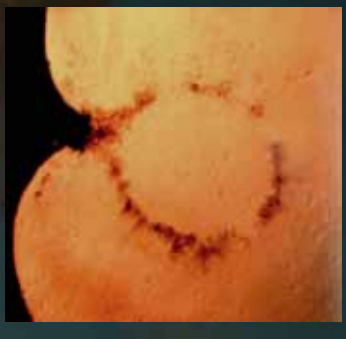
HLA-B27 related AAU - Lost treatment skills

- Introduction of prednisolone acetate:
  - Reduced rate of subconjunctival steroid injection
  - Therefore reduced usage of Mydricaine
- Under-use of atropine
- Under-use of local heat



HLA-B27 related AAU Old skills regained ?

- Break the synechiae before the patient leaves:
- Vigorous mydriasis:
  - Sub-conj Mydricaine or:
  - Gt Atr 1% + PE 2.5%
- Then apply local heat:
  - Microwaveable pads
  - Water-filled glove
- Repeat if necessary!



Can recurrent AAU be suppressed?

- Sulphasalazine
  - 10 pts with >=3 recurrences/yr – 1yr treatment
  - Annual recurrence rate 3.4 – 0.9
    - (Munoz-Fernandez S et al. J Rheumatol 2003;30:1277-9)
- Low-dose methotrexate
  - 9 pts with >+3 recurrences/yr – 1yr treatment
  - Annual recurrence rate 3.4 – 0.9
    - (Munoz-Fernandez S et al. Eye 2009;23:1130-3)

Bilateral or granulomatous AU – investigate ?

- History
  - Known medical diagnosis, treatment - detailed
  - Ask: arthropathy, bowel, chest, skin, STD, recent illness, travel
- Investigations
  - CXR - Chest CT if doubtful signs
  - ACE
  - FBC, ESR, CRP
  - Syphilis serology
  - Consider tuberculin testing if suspicious

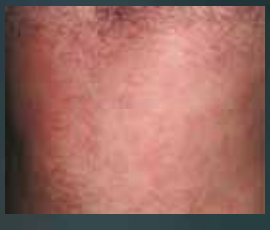
Don’t miss infective AU

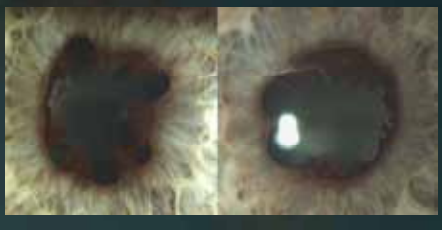
- Recently important:

- Syphilis
- Tuberculosis
- Cytomegalovirus

Syphilis

- May be anterior only
- Skin rash, headache
- Poorly responsive to steroid



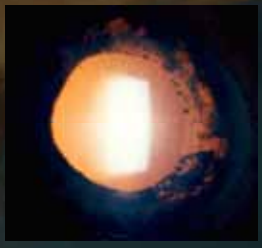


Tuberculosis

- High index of suspicion
- Mantoux + Quantiferon
- Treat all “latent” TB with uveitis
- -ve PCR doesn’t exclude

Cytomegalovirus anterior uveitis

- Immunocompetent
- Unilateral, chronic > recurrent
- Often hypertensive
- Sometimes pigmented KPs
- Sometimes iris atrophy
- Oral valganciclovir (and ? oral valaciclovir)
- ? intraocular ganciclovir



Subacute/chronic symptoms with peculiar features – investigate ?

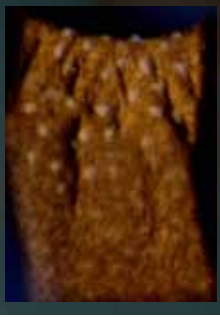
- Consider uveitis syndromes including:
  - Fuchs' heterochromic uveitis
  - Posner-Schlossman syndrome
  - Herpes simplex uveitis
  - Phakogenic uveitis
  - Non-malignant masquerades:
    - Ocular ischaemia
    - RD, Schwartz syndrome, ghost cell glaucoma
  - Malignant masquerades (very rare)

Fuchs' heterochromic uveitis

- KP morphology
- Corneal plaques

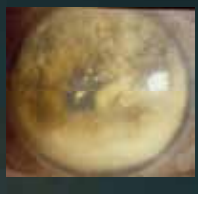
Fuchs' heterochromic uveitis

- Iris nodules
- Periocular ache
- Amblyopia



A plea to the busy ophthalmologist:

- Examination findings at presentation:
  - Are at their most distinctive
  - May never reappear in this form
  - Should be meticulously recorded
  - Consider photography



Nicholas Jones
Manchester Uveitis Clinic, The Royal Eye Hospital, Manchester, UK

Juvenile chronic arthritis and paediatric uveitis

Clive Edelsten, United Kingdom

6

Introduction

Uveitis starting in childhood has a large impact compared to adult cases: firstly, later presentation and chronicity are common leading to high complication rates; secondly ,there are rare syndromes particular to childhood that may require specialist investigation; thirdly, there are treatment considerations peculiar to children that may also require specialist advice such as amblyopia, surgical technique and immunosuppressive therapies.

Epidemiology

The incidence of paediatric uveitis is about eight times less than the incidence of uveitis in the fifth decade, when it is at is maximum. It comprises five percent of most series of uveitis patients. (Edelsten, Reddy et al. 2003)

The most common type of paediatric uveitis at a population level is idiopathic. The most common pattern in young children is chronic painless anterior uveitis, in those aged 8-16 it is intermediate uveitis. After the age of sixteen the pattern of uveitis types is similar to adulthood with acute anterior uveitis the most common. Chronic painful bilateral anterior uveitis, anterior and intermediate uveitis and panuveitis are also not uncommon in the paediatric age group.(Smith, Mackensen et al. 2009)

The most common type of systemic disease associated with paediatric uveitis is juvenile idiopathic arthritis. No other uveitis type is more frequent than 5% of cases. Even in countries with high rates of Behcet's disease, Behcet's uveitis is uncommon in childhood(Soylu, Ozdemir et al. 1997). The next commonest syndromes are sarcoid(Choi, Birnbaum et al. 2010), enthesis related arthritis and inflammatory bowel disease.

Vogt Koyanagi Harada syndrome(Garcia, Carroll et al. 2008), tubulointerstitial nephritis and uveitis syndrome(Mackensen and Billing 2009)can begin in childhood. Multiple sclerosis associated with uveitis is very rare in this age group.

There are several genetic disorders that may be accompanied by childhood uveitis. The main groups are congenital immunodeficiencies(Cohen, Lee et al. 2001) and the systemic autoinflammatory diseases: Blau syndrome(Okafuji, Nishikomori et al. 2009) and CINCA syndrome(Rigante, Stabile et al. 2010) are the most frequent syndromes with significant uveitis.

Childhood vasculitis may be accompanied by uveitis: the commoner types are Kawasaki disease, SLE scleroderma(Herrick, Ennis et al. 2010) and PAN.

Idiopathic uveitis

Chronic anterior uveitis without systemic disease is a common pattern of disease in young children. The arthritis of JIA may develop years later; investigation of renal function and sarcoidosis and possible immunodeficiency is indicated. Skin rashes are a common manifestation of sarcoid, Blau syndrome and CINCA and are easy to biopsy. Sarcoid may involve the lid margins and cornea more frequently in childhood.

Intermediate uveitis in childhood often presents late and so retinal vascular abnormalities and localized detachments are seen more frequently than in adults.(de Boer, Berendschot et al. 2006)

Multifocal choroiditis and panuveitis rarely occurs in childhood. It can be complicated by severe visual loss from secondary choroidal neovascularisation and warrants aggressive control of inflammation.

Juvenile idiopathic arthritis-associated uveitis

JIA is a group of arthritides that by definition have an onset before the age of 16. They have an association with chronic anterior uveitis. Other arthritides with an onset before the age of 16 include psoriatic arthritis, enthesis-related arthritis and rheumatoid arthritis. Only the first is associated with chronic anterior uveitis [CAU].

The ILAR classification uses a personal or family history of psoriasis, a family history of HLA-B27 related disease and rheumatoid factor to aid classification. The classification was designed primarily to aid the epidemiological study of arthritis. Antinuclear antibody and age at onset are not used in the classification but are major independent risk factors for uveitis.

Genetic studies suggest similarities between oligoarticular and polyarticular JIA in the youngest groups(Hollenbach, Thompson et al. 2010). Older children with ANA-negative polyarticular JIA may have a relatively distinct pattern of disease and appear to be at a much lower risk of CAU.

The three established independent risk factors for CAU are age at onset of arthritis [<6 years vs later], ANA-positivity, and oligoarticular onset versus polyarticular onset. Psoriatic arthritis has a risk of uveitis between that of oligoarticular and polyarticular JIA. The risk of developing CAU in those whose arthritis starts after the age of 12 appears minimal. The incidence of JIA-uveitis in the UK is 1/100,000 children.

Screening

Those with JIA developing under the age of thirteen but no other risk factors are at some risk of uveitis and should be screened– ie those who are ANA-negative, polyarticular onset after 5 years of age . Those with all three risk factors are at more than 50% risk of developing CAU. Gender, psoriasis and inflammatory bowel disease do not appear to alter the risk. The risk of CAU in systemic onset JIA appears to be very low and tends to arise within a year of onset of the arthritis.

The period of risk of uveitis appears to be related to the age at onset of arthritis and those with the earliest onset require screening for seven years from the onset [not the time of diagnosis]of arthritis. These considerations are incorporated into the UK screening programme [2006] and can be found at http://www.bspar.org.uk/pages/clinical_guidelines.asp.

Screening is the most easily achievable method for reducing visual loss. The majority of those with JIA-uveitis will unfortunately develop CAU prior to the onset of screening, or before they develop arthritis. The efficacy of various screening regimens has not been tested. Screening intervals that are so prolonged that irreversible complications can develop would seem pointless.

Clinical course of JIA-uveitis

Patients are likely to take several weeks to develop irreversible complications even when disease is aggressive: the pattern of inflammation changes slowly in comparison to other forms of uveitis. It is usually, but not universally, unaccompanied by ciliary injection or pain. There is a high rate of KP formation, flare and extensive posterior synechiae formation with early low intraocular pressure.

Heavy vitreous flare, disc oedema and extensive macular oedema accompany severe AC activity. Vitreous membranes may lead to retinal detachment. There is extensive cyclitis and chronic hypotony is far more common than in other forms of uveitis, including other forms of CAU, reflecting the prime site of inflammation seen histologically. Neovascularisation of the disc, retina and iris can occur. Band keratopathy occurs at high frequency, for unknown reasons, and may require repeated removal.

There is a high association between anterior segment complications . The posterior segment complications of macular oedema, optic disc oedema and hypotony also cluster together(Holland, Denove et al. 2009).

Time of complications

Complications are present at onset, or shortly afterwards as a result of untreated disease. Later complications may arise as a result of earlier complications such as aphakic glaucoma, or simply because of the length of time that active disease has persisted. The majority of those entering remission will have done so after 12 years.

The risk and nature of complications may therefore change through the course of the disease and the benefits of treatment regimens may alter over time. This is especially true when steroid treatment is used and where complete remission has been impossible to achieve. One quarter of the complications occur more than 10 years after the onset of disease and occur in those who have failed to achieve a significant period of complete remission before then. The risks of new severe visual loss continue for more than 15 years after the onset of disease.(Edelsten, Lee et al. 2002; Ayuso, Ten Cate et al. 2010)

Indications for treatment

With such an unusually wide range of outcomes it is important that treatment risks and costs are matched to the potential risk of the relevant patient-centred outcomes such as functional visual loss, surgical interventions and frequent hospital attendance.

Treatment goals

As complete remission is not associated with the development of new inflammatory complications an extended remission appears to be a sensible aim of treatment. Prolonged periods of low activity may precede complete remission and as it is not known what level of AC activity can lead to irreversible complications . The only evidence available suggests that there is little difference in the risk of cataract formation in those with a trace to 2+ of cells, and that cell counts are of less importance than the presence of severe levels of flare in increasing risk.(Holland 2007; Thorne, Woreta et al. 2010)

The persistence of activity is of far more significance than the actual level of activity markers at a particular point in time. Complications are more likely in those with demographic risk factors such as male gender, non-caucasian race, those with activity levels such as high AC flare, relapses with >3+ AC cells and those with prior episodes of macular oedema and hypotony. Cataract surgery increases the risk of several complications. Persistent disease, of itself, is associated with increased complications after 5 years and as does the persistent use of steroids. (Sijssens, Rothova et al. 2007; Thorne, Woreta et al. 2007; Woreta, Thorne et al. 2007; Kalinina Ayuso, Ten Cate et al. 2010; Sijssens, Los et al. 2010)

The level of disease activity one tries to achieve with immunosuppressive treatment depends on the relative risk of that eye to develop further inflammatory complications. As the affected eye develops more risk factors for losing vision, the need for tighter disease control grows. The range of risk is great – females with no complications at diagnosis may have an 80% risk of complete, complication free remission within 15 years. Males with cataract at presentation may have 50% risk of blindness over 15 years. It would seem sensible to aim to prevent the appearance of persistent flare, ocular hypertension and visually significant lens opacities in those with no complications at presentation. Whether this requires the use of systemic immunosuppression in all patients is at present unknown.

Alternative treatments to topical steroids

At some point the risks of cataract and glaucoma with continuous topical steroid treatment are sufficiently high to justify a switch to systemic steroid-sparing immunosuppression.

Topical steroids cannot treat adequately the posterior segment complications even when AC activity is controlled. A frequent cause of avoidable complications is the failure to treat vitreous haze, disc and macular oedema and hypotony with systemic treatment in patients presenting with these signs, presumably with the hope that topical treatment controlling the AC activity will be sufficient.The aim of treatment is to achieve a sufficiently long remission that withdrawal of treatment has a low risk of being followed by a recurrence. This will differ in different types of uveitis

but is likely to be of the order of 12-18 months in JIA-uveitis and may want to achieve nearer three years of remission before tailing off treatment in those who are at most risk of further visual loss. About half of patients given methotrexate [MTX] for JIA arthritis will relapse on withdrawal of treatment. Only half of patients with JIA-uveitis started on MTX will be off the drug after 7 years.(Foell, Wulffraat et al. 2010; Kalinina Ayuso, van de Winkel et al. 2011; Southwood, Foster et al. 2011)

Alternatives to methotrexate

MTX is in widespread use amongst paediatric rheumatologists because of trial data and the availability of long term safety data. It has not been compared to other immunosuppressive monotherapy in any form of uveitis. Other single immunosuppressive agents have been tried (Tappeiner, Roesel et al. 2009; Daniel, Thorne et al. 2010; Goebel, Roesel et al. 2011)There is a suggestion that JIA uveitis may respond less well to MTX than other forms of uveitis.

Inadequate control of arthritis with MTX usually leads to the addition of another drug such as an anti TNF agents and subsequent failure may lead to further combinations of biologic agents with no strong evidence base and as yet unknown long –term risks (Tynjala, Lindahl et al. 2007; Heiligenhaus, Miserocchi et al. 2011; Kenawy, Cleary et al. 2011).

The management of severe uveitis requires a clear understanding of the treatment goals, the need for occasional revision of those goals and the knowledge that many complications are not amenable to immunosuppressive therapy. It must also be made clear that where there is no trial data, there is only opinion and parents must understand that expert opinion may vary.

Cataract

Young children with uveitic cataract can sometimes do very badly with IOL implantation as there is a risk of repeated membrane formation despite apparently adequate control of inflammation. In contrast late developing cataract in JIA-uveitis may be uncomplicated. The outcomes of unilateral cataract surgery in children prone to amblyopia are poor and this is also the case in JIA-uveitis.(Sijssens, Los et al. 2010; Grajewski, Zurek-Imhoff et al. 2011)

Glaucoma

Glaucoma occurs at a markedly high rate – up to 70% following cataract surgery - and has multiple causes in this population including steroid use, persistent inflammation, aphakia and perhaps age at cataract surgery. When glaucoma develops some months after the use of steroids it is usually not simply steroid-related but every effort should be made to minimise steroid use.

Many surgical treatments have been tried including goniotomy and cycloablation. As patients may have compromised aqueous production, despite raised IOP, all procedures need caution when the eye has been severely inflamed.The use of modern tube drainage devices has greatly improved the prognosis of surgery for aphakic glaucoma. In contrast, simple steroid induced glaucoma in a quiet eye may respond well to conventional assisted trabeculectomy.

Table one: Levels of risk in juvenile idiopathic arthritis-associated uveitis summarised from the literature. Few have been confirmed in multiple sites.

1.Baseline risk factors

Male gender, non Caucasian ethnicity, ANA positive, complications at presentation

2.Additional levels of risk

A]No risk

No cells, flare, steroid treatment or ocular hypertension

B]Possible risk

Any topical steroid treatment, any AC cells, persistent activity >3m

C]Probable risk

Topical steroids more than once daily, persistent AC cells>1 + , persistent activity >3 years

D]higher risk – one of

Topical steroids more than once daily for several months, AC cells >1+ for more than 3 months, any activity>6 years, transient flare, any episode of macular or disc oedema.

E]Definite increased risk – any of

Continuous topical steroids more than three times daily, persistent AC cells>2+, persistent flare, previous surgery, multiple episodes of macular and disc oedema.

F]Extreme risk

Multiple risk factors

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Notes

Herpetic ocular disease

Marietta Karavellas, Greece

7

Herpes virus infections are a major cause of morbidity world-wide.(1). Eight different herpesviruses have been identified in humans, six of which are known to cause ocular disease: herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpes virus 8 (HHV-8). All herpes viruses are DNA viruses, and share a characteristic architecture with a central core surrounded by an icosahedral capsid. Production of infectious virus particles in the cytoplasm leads to the destruction of the infected cell. All herpes viruses establish latent, clinically silent infection in their natural hosts, during which no mature virus is produced. We do not yet fully understand the mechanisms which maintain latency, or the factors which cause reactivation and viral replication. The herpes virus family can be divided into three categories: alpha, beta and gamma, depending on their host range, cell tropism, and reproduction rate. HSV-1, HSV-2, and VZV are alpha herpes viruses, and establish latency in sensory ganglia. CMV is a beta herpes virus and remains latent in lymphoreticular cells, while EBV is in the family of gamma herpes viruses, with lymphoid tissues as sites of latency.

Epidemiology

Herpetic ocular disease is the leading cause of corneal blindness in developed countries. Of the herpes viruses, HSV and VZV are the most common ocular pathogens.

The prevalence of HSV eye disease has been reported to be 149/100,000 persons, with HSV iritis prevalence at 1.5-15/100,000 persons.

Epidemiological studies in the past have shown a high percentage of HSV-1 infection in the population, which increases with age. One report indicated that in the United States, at 15 to 25 years of age, 60% of the study population were seropositive for HSV-1, and at 60 years, 97% had been infected (2). Recent epidemiological reports suggest that in developed countries, more people now reach adulthood without having been infected by HSV-1. Accordingly, the age of presentation with herpetic ocular disease has increased, and this as well as other factors may explain the reported increase in more serious manifestations of herpetic eye disease, such as acute retinal necrosis (ARN) (3).

There has also been an increase in the incidence of genital herpes (HSV-2), with a subsequent rise in neonatal herpetic infection. (3)

Clinical characteristics

Anterior segment clinical presentations of ocular herpetic disease include blepharitis, conjunctivitis, episcleritis, scleritis, sclerokeratitis, corneal epithelial disease including dendritic and geographic keratitis, corneal stromal disease, endotheliitis, trabeculitis, iritis, keratouveitis and sclerokeratoveitis.

Posterior segment manifestations are rarer, and usually significantly more sight-threatening. These include the necrotizing retinopathies: ARN, PORN and CMV retinitis, as well as choroiditis, retinal vasculitis, and optic neuritis. Anterior segment intraocular inflammation caused by HSV 1 and 2, VZV and CMV will be presented here.

Anterior uveitis

1) Herpes simplex anterior uveitis

Herpes simplex is one of the most common infectious causes of anterior uveitis, accounting for up to 9% of all cases in some reports.

Anterior chamber inflammation occurs in up to 10% of patients with HSV keratitis, but may occur without corneal disease, or following resolution of corneal lesions. Mild iritis often accompanies stromal keratitis and endotheliitis. HSV iridocyclitis is almost always unilateral, and should be considered in every case of unilateral anterior segment uveitis.

Symptoms and signs

Patients complain of acute onset of redness, pain, photophobia and blurring of vision. A history of recurrent herpes labialis and/or keratitis may be, but is not always present.

On examination, there is a conjunctival circumcilliary injection, diffuse fine or mutton-fat keratic precipitates, and varying degrees of cell and flare reaction in the aqueous. Patchy iris atrophy with transillumination defects and elevated intraocular pressure are often present. Decreased corneal sensation, dendrites, corneal edema, or the typical disciform stromal lesion, as well as corneal scarring may be present, and facilitate the diagnosis.

Herpetic iritis in general can be focal or diffuse. Focal iritis is characterized by focal iris hyperemia and formation of circumscribed posterior synecheae leading to iris pigment epithelial defects. Diffuse iritis is much more common. It is characterized by circumferential iris hyperemia, moderate to severe anterior chamber inflammation, extensive posterior synecheae, and is often complicated by secondary glaucoma.

2) Herpes zoster anterior uveitis

Anterior uveitis occurs in approximately 50% of patients with herpes zoster ophthalmicus, usually at one week from the onset of HZO, but may also present without cutaneous lesions (herpes zoster sine herpete). It is almost always unilateral, may be mild and transient or severe, recurring, **and** can become chronic. It is more common in patients 50 years of age or older, and in immunocompromised individuals, where it may be bilateral.

Symptoms and signs

Patients note pain, redness, photophobia, and loss of accommodation. Characteristic signs include decreased corneal sensation, diffusely distributed fine or mutton-fat keratic precipitates, patchy or sectoral iris atrophy due to occlusive vasculitis of the iris vessels, iridoplegia, and elevated intraocular pressure.

3) Cytomegalovirus anterior uveitis

Relatively recently anterior uveitis due to CMV, without CMV retinitis has been described in immunocompetent individuals. (4, 5). CMV anterior uveitis is usually a unilateral, iritis or iridocyclitis which is recurrent, and in some cases becomes chronic, with symptoms and signs similar to those of HSV anterior uveitis. As we have become more familiar with this new clinical entity a wide range of clinical signs have been described, including corneal endotheliitis with coin-shaped keratic precipitates and endothelial cell decompensation, sectoral iris atrophy and pupillary changes. Ocular hypertension or glaucoma are common. CMV anterior uveitis does not seem to have pathognomonic clinical features which would allow us to definitively distinguish it clinically from uveitis caused by other herpesviruses. Ultimately detection of the viral DNA by PCR of aqueous samples confirms the diagnosis.

Pathogenesis

The pathogenesis of herpetic uveitis is not yet fully understood. Various mechanisms including viral replication, lymphocytic infiltration of the iris and ocular nerves and ischemic vasculitis seem to play a role. Much regarding the interplay between the virus and the host's immune system remains to be elucidated.

Diagnosis of herpetic anterior uveitis

The diagnosis is usually made clinically, and is based on a detailed medical and ophthalmological history and a thorough ophthalmic examination.

Herpetic etiology should be seriously considered in every case of recurrent unilateral iritis or iridocyclitis. Decreased corneal sensation, active or old corneal lesions, iris atrophy and transillumination, and elevated intraocular pressure are all additional 'clues' that should serve to point us in the direction of herpetic uveitis.

The diagnosis is confirmed by detection of viral DNA in the aqueous with the polymerase chain reaction (PCR). Aqueous is harvested via an anterior chamber tap during an episode of active inflammation. Multiplex qualitative PCR can be used to detect the presence of the virus, while real-time PCR provides quantitave measurements of the viral load. Studies suggest that viral load may be predictive of the course, prognosis and complications of the uveitis.

Detection of locally produced antibodies (Goldmann-Witmer coefficient) may also be helpful.

The differential diagnosis includes Fuchs heterochromic cyclitis, Posner-Schlossman syndrome, and other herpetic anterior uveitides.

Treatment

All forms of herpetic anterior uveitis respond well to topical steroid therapy. Cycloplegics reduce the risk of posterior synecheae formation, and topical anti-glaucoma agents are given for elevated intraocular pressure. The major problem is recurrence of inflammation, which can eventually lead to ocular complications and vision loss. For the prevention of recurrences prophylaxis with systemic and/or topical antiviral medications is used.

Oral acyclovir (800mg/day) has been shown to reduce the recurrence rate of herpetic corneal stromal disease, with a prophylactic effect for as long as the antiviral regimen continues.(6).

Notes

Smaller studies (7) and clinical experience suggest that prophylactic oral acyclovir reduces the rate and severity of anterior uveitis recurrence. Acyclovir is effective for HSV iridocyclitis, and valaciclovir and famciclovir have been used for VZV iridocyclitis. Ganciclovir (4), valganciclovir (5), and valaciclovir (8) have been reported to be effective in CMV anterior uveitis.

Complications

Secondary glaucoma and cataract are the most common complications of herpetic anterior uveitis. Various mechanisms are associated with an increase in intraocular pressure, including trabeculitis, blockage of the trabecular meshwork with inflammatory cells and debris, and corticosteroid use. Treatment includes topical anti-glaucoma medications and glaucoma surgery. Cataract formation is associated with the intraocular inflammation and/or prolonged steroid use, and is treated surgically.

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Marietta Karavellas, Greece

Notes

Other viruses and anterior uveitis: where is the evidence?

Nikos Markomichelakis, Greece

8

In recent years we have gained new insight regarding the etiology and pathogenesis of intraocular inflammatory disorders, thanks, to a great extent to the development of novel techniques which have allowed us to discover many infectious pathogens which may be responsible for these diseases.

Viruses apparently play a pivotal role, as numerous viruses have been directly or indirectly detected in intraocular fluids, in inflammatory disorders which were previously considered idiopathic. These pathogens include HSV, VZV, CMV, rubella, Epstein-Barr, human herpesvirus 6, HIV, human parechovirus, chikungunya virus, and parvovirus B19.

In the present text, we will focus on the description of novel techniques which have led to the accumulation of new information, as well as on the evaluation of these data.

The harvesting of aqueous through an anterior chamber tap is a safe and simple procedure which can be performed in the clinic. 100-200μ of aqueous is obtained with a 30 g needle under sterile conditions with the use of topical anesthetic drops. The fluid is immediately sent for analysis in oder to: a) detect and quantify antibodies against specific pathogens, and b) detect DNA of these pathogens.

Detection and quantification of specific antibodies in the aqueous is done with ELISA. In order to determine whether the antibodies present in the aqueous are the result of intraocular infection, the aqueous antibody levels must be compared with total antibody production, using the Goldman-Witmer Coefficient (GWC), described by Desmonts. Under normal circumstances this coefficient is 1. A coefficient greater than 3 is highly suggestive of elevated levels of locally produced antibodies against the specific pathogen.

$$\text{GWC} = \text{Antibody titer}\ \frac{\text{Aqueous humor}}{\text{Serum}}\ \text{X}\ \text{Immunoglobulin}\ \frac{\text{Serum}}{\text{Aqueous humor}}$$

High levels of locally produced antibodies against HSV have been detected in cases of 'idiopathic' anterior uveitis, and elevated levels of antibodies against rubella in cases considered to be Fuchs' uveitis.

This method is very quick, but presents problems regarding its specificity and sensitivity. It is possible that local antibody production is due to polyoclonal differentiation of B lymphocytes, and does not reflect the presence of virus in the eye. Additionally the sensitivity of this method is reduced in immunodeficient patients, and when aqueous harvesting was done early, prior to antibody production.

Immunoblooting is a technique with higher sensitivity and specificity, but it is slow and expensive. This method can be used with very small samples of aqueous. It can detect small fragments of proteins, and is highly specific. To date in the literature there is evidence of its use only in ocular Toxoplasmosis, it can also be used in cases of possible viral uveitis also.

Today the Polymerase Chain Reaction (PCR) is one of the most popular techniques utilized in biomedical research.

It provides a simple way to amplify a specific fragment of DNA and this technique has proved useful for the detection of infectious agents. At the end of the PCR, the amount of target DNA is increased by 1 million- to 1 billion times. Even though it has US FDA approvals only for a few pathogens related to intraocular inflammation (hepatitis C virus, mycobacterium tuberculosis, neiserria gonorrhea, chlamydia trachomatis, aspergillus galactomannan) PCR is used widely for the diagnosis of ocular toxoplasmosis, as well as for many viruses.The advantages of PCR include high sensitivity, rapid results, and good reproducibility. However, due to its extremely high sensitivity, rigorous care must be taken to avoid super-infection of the sample and false-positive results.

PCR can also produce false-negative results due to polymorphism, damage to the sample, or if there is a delay in aqueous harvesting.

Two different types of PCR are available: quantitative (multiplex) and qualitative (real time). Multiplex PCR allows us to simultaneously detect multiple pathogens, with the use of different primers. However, the presence of DNA in ocular fluids as detected by multiplex PCR does not necessarily link the specific pathogen to the disease. This problem can be solved with real-time PCR and the measurement of the viral load. In order for the specific pathogen to be considered the cause of the inflammation, a high number of copies must be detected in the sample. To date there are no studies to determine a specific minimum cut-off. It may be necessary to compare the viral load in ocular fluids to the serum viral load, as theoretically a high serum viral load could be associated with entry of the pathogen into the eye due to the disruption of the ocular barriers associated with uveitis.

In many uveitis entities viral load has been shown to be associated with disease severity, such as the development of hypertony and corneal endothelial damage in CMV anterior uveitis, and iris lesions in VZV iritis. A decrease in viral load also shows treatment efficacy.

The combination of PCR and GWC seems to increase our capability to definitively diagnose infectious intraocular inflammation.

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Nikos N. Markomichelakis
Ocular Immunology and Inflammation Service
Department of Ophthalmology, General Hospital of Athens, Athens, Greece

Recent advances in the diagnosis and treatment of scleritis

Peter Watson, United Kingdom

9

Episcleritis and Scleritis

Introduction

Although scleral inflammation is only seen in one in every 6,000 new patients the consequence of an incorrect diagnosis or inappropriate treatment can be blindness. It is therefore important that all ophthalmologists are aware of what constitutes serious disease which needs urgent treatment, and what can safely be left alone possibly without any treatment at all. This is relatively easy when the inflammation affects the anterior sclera, but is much more difficult when the posterior segment is involved. Many of those with posterior scleritis have no associated anterior scleritis, they are often young and may have few, if any, physical signs and yet these are the patients who can go blind extremely rapidly.(1)

It may seem a daunting prospect to be required to distinguish between the various forms of scleral disease, but fortunately for the patients, the symptoms are usually suggestive and almost always all the physical signs can be elicited by a properly performed careful systematic clinical and ancillary examination.

Classification

Both episcleritis and scleritis are recurrent disorders. Recurrences are often triggered by simple factors such as a viral infection or even stress. However, long-term studies have revealed that it is exceptional for one type of scleritis or episcleritis to recur in a different form.(3) As it is vital not to under-treat serious disease or over-treat benign disease it is important to identify the exact condition when the patient first presents. The most important differentiation is between episcleritis and scleritis because episcleritis rarely requires treatment (although it is usually given) and scleral disease almost always requires systemic therapy.

Episcleritis

Diffuse and Nodular

Episcleritis can be diffuse or nodular and may affect both the anterior and posterior segment of the eye. As the name implies only episcleral tissue is involved in the inflammatory process, although the conjunctival vessels and the vessels lying directly on the scleral surface become dilated as a result of the inflammatory process. It is known from fluorescein angiographic and ICG studies that the inflamed appearance results from leakage and extravasations of fluid from blood vessels in the inflamed area.(4) The reason for this dramatic and sometimes severe inflammation is unclear, nor is it known why in certain individuals the inflammatory process remains localised to one small spot, as in nodular episcleritis, whereas in others the whole of the episcleral vessels of one or both eyes are dilated and the eye looks fiery red.

Careful examination on the slit lamp is all that is required in the diagnosis of anterior episcleritis. The crucial observation is whether or not there is any underlying scleral swelling. This can usually be detected through observing the eye with the very fine beam at high magnification using the red free (green) light of the slit lamp. If the sclera underlying the inflamed episclera cannot be easily visualised then 10% Phenylephrine (or other vaso-constrictor) will blanche the superficial vessels. The area of the episcleral oedema in the inflamed area will appear yellow in red free light; an appearance rarely seen in scleral disease.

Posterior episcleritis exists but is difficult to detect even with good modern OCT or ultrasonography. This is not necessarily because the technique is poor but as the episcleral tissue is extremely thin over the posterior pole the inflammation produces very little oedema. The 'T' sign, seen with ß scan ultrasonography, detects movement of the episclera away from the scleral surface. This sign can usually be detected if there is any inflammation confirming or refuting the diagnosis.

Scleritis

Scleritis can be :

Anterior ***Diffuse or Nodular***

Necrotising — Venular occlusive, Surgically induced, Granulomatous

Necrotising — Scleromalacia Perforans

Posterior ***Diffuse or Nodular***

(Necrotising scleritis is known to occur from study of pathological specimens but cannot, so far, be reliably detected on ß scan ultrasonography)

Diffuse or Nodular scleritis

In diffuse and nodular scleritis the degree of inflammation of both sclera and its overlying episclera and conjunctiva is very much more severe than that seen in episcleritis. Severe pain, accompanies the inflammation. This characteristically wakes the patient at night and gradually improves during the day. It is caused either by an accompanying myositis or as the result of stretching of the nerves in the swollen tissue, or both. This pain is referred to the face and temple; unlike the discomfort of episcleritis which is confined to the eye alone.

Diffuse scleritis presents with severe pain, referred largely to brow and jaw and marked oedema of both the episcleral and scleral tissue. Provided it is treated quickly and intensively the condition can be brought under control within 48 hours. Nodular disease, whether single or multiple,

follows a much more prolonged course. The nodule may persist even when the disease has been fully controlled and there is no active inflammation. This makes the decision of how much and how long to continue treatment much more difficult. Systemic disease is much more commonly associated with nodular disease than diffuse, so the response to therapy also depends very much on how well the systemic disease has been controlled.

Necrotising Scleritis

Venular occlusive, Surgically induced,(SINS) Granulomatous

This is the most destructive form of scleral disease and all the diagnostic effort in the investigation of a patient with scleral disease must be directed to discovering whether this condition is present or not.

Although the onset of necrotising scleritis is almost always rapid and the pain intense, there are a few patients who present with an inflamed eye without too much pain. Destruction of the sclera in these patients takes place within the deeper layers of the sclera and so the necrotising nature of the condition can easily be missed. This makes close inspection of the vasculature with or without fluorescein and ICG angiography most valuable in distinguishing between the more benign forms of scleritis and the necrotising disease.

In ***Venular Occlusive Scleritis***, which is often associated with rheumatoid arthritis the blood within the vascular networks overlying the necrotic area becomes static even though the vessel contains blood and is dilated. As a consequence there is no perfusion of blood through the episclera in this region. The limbal scleral tissue is spared even though both the cornea and sclera may be involved. If the vascular stasis is not noticed and the causative inflammation is not suppressed, necrosis occurs and this may rapidly lead to loss of tissue not only in the sclera but in the overlying conjunctiva and episclera.

Surgically Induced Scleritis is not uncommon. It is usually recognised by the failure of post operative inflammation to settle quickly. It can occur after nay type of surgical procedure and requires urgent and aggressive therapy. If the inflammation becomes established it can be exceptionally difficult to treat

It is important to recognise ***Granulomatous Scleritis*** very early as it is almost always part of a systemic and potentially fatal Systemic Vasculitis. The physical signs of raised irregular lesions in the deep sclera and of destructive changes which transgress the limbus, are characteristic and treatment has to be aggressive

Necrotising Scleritis without Inflammation

Scleromalacia Perforans

This unusual condition almost always occurs in elderly, usually female, patients with longstanding and inactive rheumatoid arthritis. The eye is not painful but rather uncomfortable. These eyes, which have very little conjunctiva or Tenons capsule, normally appear blue/white. Either the patient or their attendant notices that the white eye has changed colour from porcelain white to yellow. The yellow spots are necrotic areas of sclera and represent a sequestrum of scleral tissue. Progression can occasionally be inhibited if treated very early but those regions which

already contain dead tissue cannot be influenced by treatment. Over time the necrotic area will be resorbed, leaving the bare choroid exposed, covered only by a thin film of fibrous tissue. Unless the intraocular pressure rises this will not be harmful and no protective covering is necessary.

Posterior Scleritis

Posterior scleritis is a very much under-diagnosed condition. The use of ß scan ultrasonography confirms that posterior scleritis is equally as common as anterior scleritis and because of the lack of visible physical signs and the proximity of the inflammation to the macula, retina and optic nerve, it is potentially devastating. Undiagnosed and untreated posterior scleritis of whatever type can rapidly lead to blindness.

Diffuse and nodular posterior scleritis

Posterior scleritis often affects young people from 5 years upwards. The diagnosis depends almost entirely on the ultrasonographic appearances. Apart from the appearance of choroidal folds, disc oedema, or, occasionally detectable peripheral posterior displacements of the choroid and retinal detachments there are no physical signs. Attention is drawn to the possibility of this disease by deterioration of vision and by pain which, surprisingly, is not always a prominent feature. Fortunately the ultrasonographic signs in these patients are typical and diagnostic and can usually be differentiated from those who have posterior episcleral inflammation alone. Diffuse posterior scleritis, if detected in young people or adjacent to the disc or macula, must be treated extremely vigorously and at once if the vision is not to be affected permanently. Scleral nodules on the other hand can often be enormous without apparently affecting vision at all.

Posterior Necrotising Scleritis

Localised areas of scleral necrosis are often seen by retinal surgeons but this is usually due to the thinning of high myopia or from infected external plombs. However although it is known from pathological specimens that inflammatory necrotising scleritis does occur it has, so far, proved impossible to be certain with any form of imaging which of the posterior lesions are the result of a severe diffuse posterior scleritis and which of these lesions are destructive.

Infective Scleritis

Infective scleritis is not uncommon. It is vital that infectious disease is eliminated by culture and if necessary scrapings before prescribing the anti-inflammatory medication needed for immune mediated scleritis If a patient with scleritis is not responding to medication the case should be reviewed in order to consider infection. The commonest organisms which affect the sclera are the Gramm negative bacilli, Fungus infections and Acanthamoeba

Treatment of Immune Mediated Episcleritis and Scleritis

Episcleritis

Whether episceritis is treated or not the condition lasts for ten days. Therefore if the inflammation is not too severe cold artificial tears, applied as required, is the best treatment.

If local steroids are deemed necessary they should only be applied for a maximum of seven days. There are more problems induced by steroids than are solved by its use in this condition

Anterior and Posterior Diffuse and Nodular Scleritis

Systemic treatment of both the systemic and the eye disease is required to treat these conditions. Most will respond to a full dose of a Non Steroidal Anti Inflammatory Drug (NSIAD). Ibuprofen and its direct derivative Flurbiprofen , have been shown to be the most effective but provided a full anti inflammatory dosage is used all (NSAIDs) will work. Treatment should continue at this dose until pain is relieved and then a lower dose used until the disease is quiescent. If there is a failure to respond to this regime or there are any sight threatening complications, particularly in posterior scleritis, then systemic streroids are required. Subconjunctival steroids can be helpful in recalcitrant cases but should be used with caution as scleral necrosis can occur at the site of injection

Necrotising Scleritis

With the exception of scleromalacia perforans which does not need treatment, necrotising scleritis of whatever variety requires intense and aggressive systemic therapy.

Prednisolone should be administered in the acute phase. This must be given in immunosuppressive dosages , initially intravenously if the inflammation is sight threatening or orally in the less severe cases. The starting dose should be 100mgm orally, the dose being reduced rapidly to an anti inflammatory dosage of 20 mgm as soon as the pain is relieved. If at all possible the drug should be withdrawn completely as soon as possible because of the unacceptable side effects.

In the later stages of the disease, if the patients fails to respond completely to steroids alone and in patients with SINS or Systemic Vasulitis disease modifying agents (DMARDs) such as cyclophosphamide and metotrexate will have to be added. If these are needed it is strongly recommended that colleagues who are familiar with the use of these drugs should be consulted

Biologic agents such as Infleximab are now becoming widely available. They are extremely effective in controlling disease which has failed to respond to other therapy. Because of the cost and the potential side effects they are at present the treatment of last resort but we have now reached the situation where if the disease is detected early and correctly diagnosed no one should lose vision from scleral inflammation alone.

Conclusion

Scleritis, although relatively uncommon, is a severe sight threatening disease. It is, however, easy through careful history taking, clinical and ultrasonographic examination to separate those who require urgent and aggressive therapy from those who require little or none.

Modern treatment can be administered without side effects in the great majority of patients and even those whose have extremely severe disease can now be treated. To be successful the disease must be seen, correctly diagnosed and treated early . If this is done blindness from this condition is a thing of the past.

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Peter Watson, United Kingdom

Toxoplasmosis and parasitic infections

Carlos Pavésio, United Kingdom

10

Introduction: even though the most common cause of posterior retinitis in the world is a *protozoan (T gondii)*, the majority of the other parasitic infections will be rarely seen in a normal practice in the UK or in the US. However, it is important to recognize them since with the increased facility in travelling we are, more then ever, likely to be confronted with a patient coming from areas where such infections are highly prevalent. This knowledge will help avoid unnecessary investigations and establish a therapeutic plan, which may result in cure or control of the inflammatory process triggered by the presence of the parasite. I will review here the most common parasites, which have been implicated in retinal disease.

TOXOPLASMOSIS

Toxoplasmosis represents the most common form of posterior uveitis worldwide, with higher prevalence in tropical areas. Even though the etiological agent, *Toxoplasma gondii*, was identified at the beginning of the last century, a better understanding of its life cycle, establishing the cat as its definitive host, and others aspects of its interaction with the host, have only been identified in the recent past.

Toxoplasma gondii belongs to the phylum Protozoa, and is an obligatory intracellular parasite. Sexual reproduction occurs in small intestinal epithelial cells of the cat, with the consequent elimination of *oocysts* in the cat's faeces. It will take at least 2 days for the oocyst to sporulate and become infective, a process, which depends on ambient temperature. Once ingested by other animals (intermediate hosts), the oocysts will rupture and release organisms that will transform into *tachyzoites*, which will ultimately lead to the formation of tissue cysts, packed with *bradyzoites*.

Transmission occurs by ingestion of any of these forms of the organism, which depends on hygienic and alimentary habits. The disease can also be acquired by transfusion of whole blood or leukocytes, organ transplant or accidentally, in laboratory workers.

Ocular toxoplasmosis is commonly attributed to congenital infection, but the role of acquired infection appears to be more important than previously thought. Lesions seen in the retina may actually be more frequently the result of a remote acquired infection rather than a late manifestation of a congenital transmission. The evidence available suggests that at least two thirds of ocular toxoplasmosis is caused by postnatal infection. High levels of exposure to contaminated meat, such as reported in Southern Brazil, has been identified as a possible explanation for high prevalence of toxoplasmic scars in that population and to the occurrence of disease in several siblings (not possible by congenital infection). More recently it has been found, in another part of Brazil, that contamination of water supplies may play an even bigger role in the transmission of the disease to the community.

Congenital transmission occurs only when the infection is acquired during pregnancy. The risk of transmission depends on the stage of pregnancy during which the mother becomes infected. It is highest during the third trimester (60%), with a smaller risk during the first (15%) and second (30%) trimester. The foetus is at highest risk for serious complications during the first trimester, but most of the cases of ocular disease result from infection during later stages.

Toxoplasmic retinochoroiditis is the most common manifestation of congenital disease, occurring in 70% to 90% of all patients with congenital toxoplasmosis. It occurs more frequently in patients who develop neurological disease when compared with those with disseminated disease at birth. Even though a high percentage of children may appear normal at birth, the majority will develop ocular toxoplasmosis over time.

Primary ocular disease occurs more frequently during acute systemic infection, but may also occur during the course of the chronic phase of systemic disease. Case reports show that new lesions can appear for the first time as early as 2 months after onset of infection, or as late as 5 years. Recurrences are typical of both the congenital form and of the chronic phase of postnatally acquired disease. The risk of recurrence of lesions in cohorts of prenatally infected children and case series of patients with postnatal disease appear to be similar (8-40%), but are based on small numbers.

The classical ocular lesion is a focal necrotizing retinitis, with overlying vitreous inflammatory haze. This lesion is most likely caused by actively replicating organisms released form a ruptured cyst. The inflammation of the choroid and anterior segment are secondary, and probably due to direct extension of the retinal inflammation or a hypersensitivity reaction. Recurrent retinal lesions occur at the borders of retinochoroidal scars (satellite lesion). A bilateral macular lesion is suggestive of congenital disease, and unilateral lesions can be a consequence of both acquired and congenital disease. These lesions lead to destruction of the retina and underlying choroid resulting in scars, which will progressively show accumulation of pigment.

In the early stages of newly acquired disease patients may present a picture of retinal vasculitis in the absence of a visible focus of retinitis, but many of these patients will later develop lesions consistent with toxoplasmic retinochoroiditis in the same eye, suggesting the presence of the parasite in retinal tissue during the initial episode.

The symptoms from posterior disease include floaters and blurring of vision, while pain and redness will occur as consequence of anterior segment involvement. Retinal vascular involvement is frequently seen, with sheathing of vessels occurring even far from the original lesion. Vascular occlusion is not common, but may occur when a vessel crosses the main focus of inflammation.

Variations from the classical lesion include outer punctate lesions and also neuroretinitis. More recently it has been reported that retinal vasculitis, with vitritis and anterior chamber reaction,

may be the only ophthalmic findings in the early stages of a newly acquired infection, but most of the patients in this series later developed retinal lesions, which probably indicates that the initial inflammation is already related to the presence of organisms in the eye, probably in the retinal tissue.

Loss of vision may occur as a consequence of lesions affecting the macula, optic nerve, or retinal detachment secondary to organisation of a heavily infiltrated vitreous. Other complications involve subretinal neovascular membranes, which occur at the borders of scars, and may also affect vision if in the macular area. Anterior segment complications include cataract, posterior synechiae and glaucoma.

The disease is more severe and tends to have a very different clinical behaviour in immunosuppressed individuals, such as in AIDS. Multifocal, bilateral or extensive areas of necrosis can be seen.

Pathogenesis of ocular toxoplasmosis depends on the virulence of the Toxoplasma strain and the host's immune response. The reason for recurrences is not entirely clear with many theories including rupture of tissue cysts, hypersensitivity reaction or autoimmune mechanisms. The presence of tachyzoites seems to be very important in the genesis of retinal lesions, but the importance of retinal autoantibodies and peripheral lymphocyte reactivity to S-antigen in vitro remains uncertain. Control of infection is dependant on cellular immune response with a complex participation of macrophages, CD4 and CD8 lymphocytes, and many cytokines. The possibility of tolerance developing after congenital disease has recently been raised.

The diagnosis is mainly clinical, with serological tests used to confirm previous exposure to the organism. The tests most frequently used are the Sabin-Feldman dye test, indirect fluorescent antibody (IFA), ELISA and agglutination tests. The dye test is the gold standard, but involves the use of live tachyzoites, which makes it less practical. The IFA has comparable sensitivity and specificity, but it is easier, safer and less expensive. ELISA sensitivity and specificity depend on the commercially available tests.

In atypical cases, such as seen in immunocompromised individuals, the need for confirmation of etiological diagnosis becomes more important. Diagnosis can be confirmed by isolation of *T gondii* from body fluids or tissue specimens, histological demonstration of organisms in fluids or tissue specimens, and polymerase chain reaction (PCR) techniques for detection of *T gondii* DNA.

The use of fluorescein angiography is especially useful in evaluating vascular complications associated with acute lesions and also in the diagnosis of cystoid macular oedema. The use of Indocyanine Green angiography has been recently use to study toxoplasmic retinitis and has shown choroidal vascular abnormalities which may be very helpful in the understanding of the pathogenesis of this retinitis.

Therapy is indicated for lesions threatening central vision (macula and optic disc) or for very exudative lesions leading to intense vitritis. Several antimicrobial agents have been used in the treatment of toxoplasmic retinochoroiditis, without any striking benefit of one over the other being demonstrated. None of the agents seems to efficiently affect the tissue cysts and for this reason none of them can prevent recurrences. The most frequently used therapy is the association of Pyrimethamine and Sulfadiazine. Other options include Clindamycin, Spiramycin, Tetracyclines, Azithromycin, Clarithromycin and Atovaquone.

In immunocompetent hosts systemic steroids are used in association with antimicrobial agents, since the intense inflammatory reaction is probably the most important factor in tissue damage. Treatment will last for 4 to 6 weeks, or according to clinical response, which is directly linked to the size of the retinal lesion. All these drugs have potential serious side effects and close monitoring of blood parameters is needed. Treatment of anterior segment inflammation is done accordingly with topical steroids and cycloplegic agents.

In immunocompromised individuals systemic steroids are contraindicated, since the damage is mainly caused by replicating organisms, with minimal inflammatory component. In these patients maintenance therapy is necessary due to the high risk of reactivation of the infection. The situation will change pending on reconstitution of the immune response.

There is no clear evidence that the therapeutic regimes had a beneficial effect on the outcome of active lesions. The available randomised clinical trials comparing different forms of therapy do not show any significant difference and the improvement demonstrated may have been simply the effect of systemic steroid therapy used. Recent data suggests that the prolonged use of anti-toxoplasmic therapy may produce protection against recurrences not only during the period when the drug is used, but also for many years after it has been discontinued.

Active recurrent lesions during pregnancy do not pose a threat to the foetus, and the mother should be treated according to the same indications as above, but keeping in mind the potential risk of teratogenesis of the antimicrobials, especially during the early stages of pregnancy. Spiramycin is a large molecule, which tends to concentrate in the placenta, with minimal crossing occurring, and represents a good option in these cases.

Prevention is aimed at breaking the transmission cycle. Better hygiene and proper cooking of meat are important in this process. Ingestion of properly treated water is also important. The development of vaccine utilising a major Toxoplasma surface antigen is another possibility. In AIDS patients drug prophylaxis becomes important for those who are seropositive and have reached a low level of immunity.

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TOXOCARIASIS

This parasitic disease is caused by the ascarid (roundworm) *Toxocara canis*. It has a high prevalence, greater than 80%, in puppies of 2-6 months of age, dropping to 20% in dogs older than 1 year. It is estimated that around 20% of dogs are infected in southern England.

Children and adults acquire the infection by accidental ingestion of eggs which are eliminated in dogs faeces. The majority of infected patients have a history of geophagia or other forms of pica (ingestion of clay or grass). Seroprevalence varies from 2.6% and 14.6% in places like London and Bedfordshire, to 92.8% in places with higher exposure. Humans are not the definitive hosts, and infestation with the second or third stage larvae causes two diseases: a systemic form called Visceral Larva Migrans (VLM), ando ocular toxocariasis.

VLM is a systemic acute form, which occurs in younger children and is characterised by fever, pallor, hepatosplenomegaly, coughing or wheezing, anorexia and weight loss. It happens in the setting of a large larval load, serving as a massive antigenic stimulus, which induces an intense immune response with marked eosinophilia.

Ocular toxocariasis is attributed to the presence of the parasite in the ocular tissue. It occurs in cases of low larval dose, insufficient to stimulate the immune system, allowing the passage of the larvae through the liver into the general circulation, eventually reaching the eye. The ocular form is typically unilateral and 80% of the cases occur before the age of 16. The clinical spectrum has been devied into three major manifestations: a choroidal granuloma of the posterior pole, a peripheral chorioretial granumola and endophthalmitis. The granulomas are the result of a second stage larva in the choroid.

Children will present to the ophthalmologist either because of ocular inflammation or because of poor vision due to retinal abnormalities or cataract. When direct examination is not possible, A-scam and B-scan ultrasonography are of considerable value especially in the differential diagnosis with retinoblastoma.

The ELISA is the most reliable test, using two Toxocara-derived antigens. A titer greater or equal to 1:16 has been suggested to maximize sensitivity and specificity. Aspirates from aqueous and vitreous allow for both cytological analysis of the predominant cell type and for the detection of local production of antibodies by the ELISA test. The definite diagnosis is only possible by demonstration of the larvae in the ocular tissue.

The differential diagnosis includes Coates' disease, persistent hyperplastic primary vitreous (PHPV), retinopathy of prematurity and pars planitis.

The aim of therapy is to reduce intraocular damage caused by the inflammatory reaction. Topical steroids are very useful in the management of anterior segment inflammation and periocular

injection of long-acting depot corticosteroid is a good option in cases of mild inflammation of the posterior segment. In cases of severe and diffuse inflammation, systemic steroids are necessary. The use of antihelmintic agents is controversial since the death of the parasite could induce significant inflammation, Vitrectomy may be necessary to release vitreous traction and repair tractional or rhegmatogenous retinal detachments. Visual prognosis depends on severity and location of the anatomical changes.

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DIFFUSE UNILATERAL SUBACUTE NEURORETINITIS (DUSN)

This syndrome was originally described under the name of “unilateral wipe-out syndrome”, which was due to the end-stage appearance of diffuse retinal atrophy and a pale disc. In 1977 Gass reported 29 patients with findings characteristic of the “diffuse unilateral subacute neuroretinitis” at the Lang Lecture to the Royal Society of Medicine, and he identified an intra-retinal nematode in two additional patients before the Lecture had been published. Since then many reports have appeared with the recognition of an intra-retinal or sub-retinal organism as the cause of this condition. A recent report from Brazil describes the first, and so far only, case of bilateral retinal involvement.

The initial reports came from the southeaster part of the USA, but soon reports from northern USA and also Caribbean region, South America, Canada, Europe and China, have been published.

The organisms associated with this condition are nematodes. Two different sizes of larvae have been identified in these reports. A smaller larvae, measuring between 350 and 700 µm in

length, appears endemic to the south-eastern USA, Caribbean islands and Brazil, while a larger nematode, measuring 1500 to 2000 µm in length, has been described in the northern midwestern USA, Canada and China (a case of a large nematode has also been reported from Brazil). The smaller nematode could be *Toxocara canis*, or *Ancylostoma canimnum*, while the larger organism has been more frequently reported to be *Baylisascaris procyonis*, a common intestinal roundworm of lower carnivores, especially racoons and skunks. It is obvious that other nematodes may be associated with this type of presentation and that this will be greatly influenced by the geographical occurrence of cases.

Clinical characteristics of patients at presentation: patients are usually healthy and complain of ocular discomfort, transient visual obscuration, visual loss of varying intensity, central or paracentral scotomas, vitritis, papillitis, and crops of multiple evanescent, gray-white outer retinal lesions. The anterior segment is usually spared, even though reports of more intense inflammation, including hypopyon, have appeared. The vitreous involvement is usually mild, but more intense reaction may also be seen. The clustered retinal lesions tend to resolve within 10 days, and a new area of a new cluster of lesions may then appear. These are the areas where it will be possible to find the subretinal nematode, which occurs in less than 50% of the cases. The best method of visualization of the subretinal nematode is fundus examination with a 78 or 66 diopter lens or the use of the fundus camera. Recently the SLO has been used to identify the organisms and several advantages were listed including the possibility for several physicians to see the fundus simultaneously, better contrast and better adjustment of settings for examination of areas of special interest.

Late features include narrowing of retinal vessels, optic nerve atrophy, and focal or diffuse atrophic changes in the retinal pigment epithelium. The damage to the retina seems to be due to a combination of the presence of excretory-secretory products, including enzymes and metabolic wastes produced by the nematode, which will have local toxic effects and will also generate an inflammatory response, especially mediated by eosinophils that will degranulate other toxic substances locally.

The differential diagnosis will vary depending on the stage of the disease. In the early stage, the disc swelling may be misdiagnosed as papilledema, papilits or retrobulbar neuritis (depending on the visual acuity and pupillary reflex). The outer retinal lesions may resemble those of APMPPE, evanescent white dot syndrome, multifocal toxoplasmosis and the pseudo presumed ocular histoplasmosis syndrome. In the late stages, the unilateral atrophic disc may be confused with intra-cranial or retrobulbar lesions. The RPE changes may be confused with unilateral RP, post-traumatic chorioretinopathy, or chorioretinal atrophy after ophthalmic artery occlusion.

Investigations attempting to find a systemic abnormality are usually negative. Electroretinography will show abnormalities even in the early stage, and will rarely be extinguished. Goldman perimetry is useful to evaluate visual field loss before and after treatment.

Laser treatment of the nematode at any stage of the disease is the preferred therapy for those cases where the nematode could be found. Surgical removal of the nematode via pars-plana vitrectomy and retinotomy has been reported in one case, but this was an exception. Albendazole, 400mg/day for 30 days should be attempted in cases where the organism cannot be seen and the disease is clearly progressing and also when the vitreous reaction is more intense, which is reflecting a more severe damage to the blood-retinal barrier allowing better penetration of the drugs into the eye. Corticosteroids may provide transient suppression of inflammation but are unable to alter the final outcome.

Early recognition of the condition and identification of the parasite is the key for the visual prognosis, which will otherwise be extremely poor.

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CYSTICERCOSIS

This parasitic disorder is caused by the ingestion of the eggs of *Taenia solium*, which are excreted in human faeces. It is characterized by involvement of multiple organs by the embryonic form of the organism, *Cysticercus cellulosae*. It is important to differentiate between teniasis and cysticercosis. In teniasis the disease is caused by the presence in the small intestines of the adult form of Taenia. The species most frequently associated with human disease are *T saginata* and *T solium*. Man is the definitive hosts and the intermediate hosts are the bovines for the first and the swines for the second. The adult form causes very little trouble to the host, but the larval stage will produce significant pathology. They will establish themselves in the most vascularized tissues including heart, muscles, brain, eyes and sub-cutaneous tissue. Neurocysticercosis is the most frequent neuroparasitosis in the world.

Teniasis caused by *Taenia saginata* affects around 77 million people worldwide, especially in Africa, Asia and South America. *Taenia solium* affects 2.5 million people and 300.000 are affected by cysticercosis. Cysticercosis is endemic in Latin America, Asia (China, India, Indonesia), and also in Portugal, Spain, Poland and Rumania. It is especially associated with poor hygiene.

Man can acquired cysticercosis by one of three possible ways:

1. Ingestion of eggs in contaminated water or food
2. External autoinfection – hand-mouth
3. Internal autoinfection – retroperistaltic movements allowing the proglotes to reach the stomach liberating the oncospheres.

The eye involvement may involve intra ad extra-ocular structures. The subconjunctival location is the most frequent one for the extra-ocular form (90%), followed by orbit (7%) and lids (3%).

The intraocular location may involve the anterior chamber, choroid, subretinal space, vitreous.

Live organisms of small size usually elicit very minimal inflammatory response. The death of the organism will lead to the release of antigens, which will produce an intense inflammatory response.

Ocular cysticercosis is treated with anti-inflammatory therapy with systemic steroids. Surgical therapy is indicated for those cases of cysts in the anterior chamber and for those in the vitreous cavity or sub-retinal space.

ONCHOCERCIASIS

Also known as river blindness it is am insect borne disease caused by the filarial nematode *Onchocerca volvulus*. It is transmitted from person to person by black-flies. The name river-blindness comes from the fact that the black-fly vector breeds in fast flowing rivers and transmission is generally limited to those people who live or work near the rivers.

It is endemic in 34 countries, with about 18 million people globally infected, of whom 99% are in Africa. A further 120 million people worldwide are at risk of developing the disease, 96% of whom are in Africa.

Onchocerciasis causes severe skin disease, but it is the blindness that represents the most important aspect of this condition. Of the 18 million infected an estimated 270,000 are blind and 500,000 severely visually disabled.

The infective worms enter the body through the black-fly bite and develop into mature adult worms (macrofilariae). The adult worms produce millions of microfilariae, which migrate throughout the skin, during their lifetime, which lasts up to 14 years. The microfilarias induce the pathology characteristic of the disease, including chronic dermatitis and skin atrophy, lymphadenitis and fibrosis, and ocular inflammation. The actual route of entry of the microfilariae into the eye is not known but the proposed routes include the sheaths of the posterior ciliary arteries and nerves, the blood circulation, the CSF and along orbital septum and the cheek ligaments. Microfilariae can be seen in the cornea or the anterior chamber by slit-lamp examination. Onchocercal eye disease develops after a long exposure to onchocercal infection, although eye lesions tend to appear in individuals between the age of 30 and 45 years and are usually more commonly seen in males who work outdoors.

Wolbachia are bacterial symbionts of the major human filarias, including *Onchocerca volvulus*. They belong to the order of Rickettsiales and are found in the body wall (hypodermis), in oocysts, in all embryonic stages, and in microfilarias. It seems that *Wolbachia* has become essential for the fertility of the adult worms, and are transmitted transovarially to the next generation, in a similar way to mitochondria. A recent study has shown a significant association between adverse reactions after microfilaricidal treatment and elevated concentrations of *Wolbachia* DNA. The endotoxin-like products of Wolbachia constitute a major proinflammatory stimulus in the eye. The information available shows that *Wolbachia* are major contributors to the immunopathology of onchocerciasis and become obvious targets for new therapeutic regimens.

The main pathways to blindness due to onchocerciasis are sclerosing keratitis, chorioretinitis and optic nerve disease, which actually accounts for most of the blindness secondary to posterior segment disease. Other reasons for visual loss include, iridocylclitis leading to secondary cataract or secondary glaucoma.

The control of onchocerciasis has been based at various times on large scale nodulectomy, vector control or large scale chemotherapy. The chemotherapeutic agents used prior to 1987 were suramin and diethylcarbamazine (DTC). Suramin was a good macrofilaricidal drug but required intravenous infusions and was nephrotoxic. DTC is a microfilaricidal drug, was associated with the development of the Mazzotti reaction. This was shown to precipitate and accelerate the progression of optic nerve disease in individuals with a heavy onchocercal infection.

Ivermectin is also a microfilaridal drug, but it has also been shown to inhibit the release of microfilariae from adult worms. The end result of these actions is a reduction in microfilaria loads, prevention of progression of lesions in the eye, potentially preventing blindness.

Recent studies have shown that at least in Africa, this approach may not be stopping transmission. Even though ivermectin acts rapidly to reduce the number of skin microfilarias, it does so for only a few months, after which they reappear at levels of 20% or more of pre-treatment numbers within a year, what is sufficient for transmission to continue.

A new approach is to target the bacterial symbiont. Depletion of *Wolbachia* in some studies has shown a disruption of embryogenesis in female worms. A partial microfilaricidal activity has also been reported, and this effect seems to be also associated with depletion of the bacteria. So far, tetracyclines, rifmapicin and chloramphenicol have shown activity against *Wolbachia* in vivo, and azithromycin has shown activity in vitro. Studies with doxycycline 100mg/day for six weeks, has shown depletion of *Wolbachia* followed by an interruption of embryogenesis in worms lasting for 18 months. The problems for mass treatment are the prolonged course of therapy (6 weeks with 100mg/day and 4 weeks with 200mg/day), and the known contraindications to doxycycline (pregnancy, nursing and children up to 9 years). We still wait for the final answer to this problem.

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SCHISTOSOMIASIS

Schistosomiasis (synomnym: bilharziasis) is a systemic parasitic disease caused by trematode flatworms of the genus *Schistosoma* that causes significant morbidity and mortality in humans. The five major agents are *S. mansoni*, *S. japonicum*, *S. haematobium*, *S. mekongi* and *S. intercalatum*, each one more prevalent in several regions of the world. It is a worldwide public health problem, affecting over 200 million people in 74 countries. Of these, 120 million have symptoms of the disease and 20 million have severe consequences. In many areas, schistosomiasis infects a large proportion of children under 14. An estimated 650 million people worldwide live in endemic areas.

Scshistosmiasis presents distinct clinical stages: cercarial dermatitis, acute and chronic disease.

Cercarial Dermatitis

When the cercariae penetrate, the skin, one may note a prickling sensation and note a macular rash several hours later. This condition is more severe in previously sensitized persons.

Acute schistosomiasis

Also called Katayama fever, occurs in previously uninfected persons from nonendemic areas in 2 to 8 weeks after initial exposure, especially to *S. japonicum* or *S. mansoni*. Acute fever accompanied by chills, headache, myalgia, abdominal pain, diarrhea, cough, and bloody stools develops often. Hepatosplenomegaly and lymphadenomegaly are also seen. Symptoms and signs disappear in a few weeks. Eosinophilia is almost always found.

Chronic schistosomiasis

Signs and symptoms may vary according to the extent of the infection, dissemination of eggs and development of granulomas. Virtually, any organ may be affected. Most common sites are the bowel, lungs, liver, spleen and bladder (*S. haematobium*). An important hallmark of the disease is the portal vein hypertension, seen in hepatosplenic schistosomiasis, which leads to splenomegaly, hypersplenism and development of portosystemic collateral blood vessels.

Ocular Disease

Ocular involvement is rare. Schistosomotic conjunctival granuloma, orbital schistosomiasis, intraocular worm, iridocyclitis and inflammation of the retinal pigment epithelium and multifocal choroiditis are reported in the literature.

Etiology and Pathogenesis

Transmission of schistosomiasis requires an appropriate snail as intermediate host, contamination of still water and human entry into the snail-infested water.

Adult worms measure 1 to 2 cm in length and 0,3 to 0,6 mm in width. *S. mansoni*, *S. japonicum*, *S. mekongi* and *S. intercalatum* live in the portal and mesenteric vessels while *S. haematobium*, in the vesical plexus. Eggs and are deposited in the venules and make their way into the urine or feces. In the water a 0,1mm ciliated larva (miracidium) eclodes and penetrates the body of the appropriate snail (its intermediate host). Within 4 to 6 weeks, hundreds of motile cercariae measuring 0,1 to 0,2 mm emerge. The cercariae penetrate human skin with the help of their glandular secretions, changing into schistosomula, which migrate to the lungs and liver, and in about 6 weeks, mature to adult worms and descend via the venous system to their final habitat. The disease is largely due to host's immune response to the larvae and eggs. It includes granuloma formation, initially consisting of neutrophils, eosinophils and mononuclear cells and later mostly lymphocytes, macrophages, multinucleated giant cells and fibroblasts.

Diagnosis

The clinical suspicion of schistosomiasis must be confirmed by direct or indirect laboratorial exams. Direct methods include the microscopic analysis of stools or urine and rectal or bladder biopsy. Eggs appear in feces or urine about 4 to 6 weeks after cercariae penetrate the skin. Because eggs may be passed intermittently or in small numbers, repeated examinations or concentration procedures, may be needed.

Serologic tests for antibody detection may also be used.

Differential diagnosis

The ocular disease must be differentiated from milliary tuberculosis, sarcoidosis and choroiditis.

Treatment

Treatment is indicated in everyone with schistosomiasis. Successful treatment prevents the complications and, if administered early, can reverse intestinal lesions, periportal fibrosis and other lesions. The first choice for the treatment of systemic and ocular schistosomiasis is praziquantel. After a single treatment, cure is achieved in 65-90% of the cases and egg excretion is reduced in more than 90%. Oxamniquine may be used as an alternative drug with similar effectiveness of praziquantel. Oral corticosteroids should be used in severe systemic cases and topically or orally in ocular disease. Surgical excision must be needed if a worm is intraocular or in orbital location.

Prognosis

Ocular schistosomiasis has a good visual prognosis, depending on the extent of the inflammation and location of the granuloma. Systemic disease, as mentioned above, may have either a good prognosis if the infection is mild and treatment given early or a poor prognosis with high morbidity and mortality.

Carlos Pavésio, United Kingdom

Notes

Tuberculosis (TB) and Venereal syphilis

Philippe Kestelyn, Belgium

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VENEREAL SYPHILIS

Introduction

Syphilis, a sexually transmitted disease, is a systemic infection caused by a gramnegative bacterium, Treponema pallidum subsp. pallidum, a member of the order Spirochaetales, family Spirochaetaceae, and genus Treponema. T. pallidum enters the body through small abrasions on the skin or mucous membranes. After local multiplication the treponemes will spread to the regional lymph nodes and from there to the whole body. Vertical transmission via transplacental infection from the infected mother to the unborn child occurs after the first three months of pregnancy and may result in intrauterine death or give rise to congenital syphilis.

Epidemiology

The World Health Organization (WHO) estimated that there were approximately 12 million new cases of syphilis among adults in 1999. Although the disease is present in all parts of the globe, the highest incidence is recorded in the developing world with 4 million new cases in sub-Saharan Africa, 4 million in South and Southeast Asia, and 3 million in Latin America and the Caribbean. Data on the prevalence of the disease are gathered from studies of genital ulcerative diseases (GUD) , from serological screening of pregnant women in antenatal clinics and from screening of blood donors and different populations at risk (truck drivers, commercial sex workers). Using polymerase chain reaction (PCR), syphilis was found to be the cause of GUD in 10.6% of HIV negative men in South Africa and in 10% of patients in Pune, India. In antenatal clinics a highly variable prevalence is found with figures ranging from 2.5% in Burkino Faso to 17.4% in Cameroon. The prevalence of sex workers ranged from 11.6% in Singapore to 32% in Papua New Guinea. In contrast, the incidence rate in most industrialized countries is below 5 per 100 000.

Clinical manifestations

The natural history of untreated acquired syphilis has been divided into four stages: primary syphilis, secondary syphilis, the latent stage, and tertiary syphilis.

Primary syphilis is characterized by the presence of a single, painless, non-suppurative ulcer with a hard base, the syphilitic chancre. This highly infectious lesion appears 2 to 6 weeks after exposure and heals within 3 to 6 weeks. Proliferation and spread to regional lymph nodes causes painless lymphadenopathy. Most chancres are located in the genital area, but extragenital chancres on sites such as the conjunctiva and the eyelids have been reported.

If no appropriate antibiotic treament is given, the treponemes disseminate in the blood and signs of secondary syphilis appear about 6 weeks after the appearance of the primary chancre.

Secondary syphilis is characterized by a flu-like illness with sore throat, arthralgias, myalgias, headache, fever, and very often a painless, maculopapular skin rash. The rash disappears spontaneously after some weeks. Invasion of the central nervous system occcurs in about 40% of patients with secondary syphilis. Acute meningitis is observed in only 1% to 2% of patients. Neuro-ophthalmological manifestations of secondary syphilis include optic neuritis, optic perineuritis, or cranial nerve palsy. Anterior uveitis is the most common eye finding in this stage and was reported to occur in about 5% of syphilitic patients before the introduction of penicillin.

The latent stage is divided in the early latent stage, the first year following infection, and the late latent stage, the subsequent period. During the early latent stage relapses of scondary syphilis are still possible. In the late latent stage clinical disease is no longer detectable and the patient is no longer contagious, although dormant treponemes may be present in liver and spleen. Reawakening and multiplication of dormant treponemes in one third of the patients sets the stage for the development of tertiary syphilis. This may happen from several years to several decades after the secondary stage. Tertiary syphilis is divided in three groups: benign tertiary syphilis, cardiovascular syphilis, and neurosyphilis.

Benign tertiary syphilis is characterized by gumma formation. Gumma are granulomatous lesions mainly found in skin and mucous membranes but also described in the uveal tract. Cardiovascular syphilis is the result of an obliterative endarteritis of the vasa vasorum of the aorta and causes aortitis, aortic aneurysms, and aortic valvular insufficiency.

Neurosyphilis includes meningovascular syphilis and parenchymatous neurosyphilis. Meningovascular syphilis is the result of small-vessel endarteritis and vascular occlusion leading to stroke syndromes or seizures. Visual field defects due to vascular occlusions affecting the visual pathways are commonly seen at this stage. Parenchymatous neurosyphilis is the endresult of postinflammatory neuronal degeneration: general paresis, tabes dorsalis, optic atrophy, and pupillary disturbances (Argyll Robertson pupil) are all manifestations of parenchymatous neurosyphilis.

Congenital syphilis causes intrauterine death in one half of infected fetuses. In those children who survive congenital abnormalities, mainly mucocutaneous lesions and osteochondritis, may be obvious at birth (early congenital syphilis). In others congenital infection may not be apparent until about two years of age when facial and tooth deformities develop (late congenital syphilis). Interstitial keratitis is a common inflammatory sign of untreated late congenital syphilis and is, together with peg-shaped upper central incisors and sensory deafness part of the classic triad of Hutchinson.

Ocular manifestations of syphilis

Ocular involvement in primary syphilis is rare and mainly limited to chancres of the eyelids and the conjunctiva due to direct inoculation from contaminated fingers or secretions. The protean

manifestations of ocular syphilis affecting all structures of the eye occur mainly in secondary and in tertiary syphilis. Despite the widespread but erroneous belief that ophthalmic lesions are signs of tertiary syphilis, corneoscleral, uveal, retinal, and optic nerve inflammation may be observed as well in secondary as in tertiary syphilis. There are however differences: chronic gummatous or granulomatous inflammation of the ocular structures is typical of late stage disease, whereas more aggressive inflammation (iridocyclitis with vascularized nodules or roseolae and necrotizing retinitis) is associated with early disease. It is important to stress that many patients who present with ocular signs of syphilis do not have systemic signs of the disease. In fact the ocular manifestations in secondary syphilis often occur up to 6 months after the initial infection when most systemic manifestations such as the skin rash have already resolved. Only half of the patients with ocular manifestations in the tertiary stage have concomitant non-ocular signs of disease.

Anterior uveitis

Anterior uveitis in secondary syphilis starts as an acute unilateral iridocyclitis. The severity may range from mild nongranulomatous to severe, granulomatous disease. The second eye becomes involved in about one half of the patients. Typical of secondary syphilis but rarely observed are the iris roseolae which are vascular tufts in the middle third of the iris surface, corresponding to the infectious mucocutaneous lesions. In tertiary syphilis the anterior uveitis may be chronic and granulomatous (Koeppe and Busacca nodules). Gummas of the uveal tract can mimic iris tumours and even erode through the sclera. Poor response to topical steroid treatment and a history of a skin rash in the recent past should alert the clinician to the possibility of syphilitic anterior uveitis.

Posterior segment involvement

Unlike other infectious agents that have a predilection either for the retina (cytomegalovirus) or for the choroid (M. tuberculosis), treponemes seem to be able to thrive in all the layers of the eye, resulting in a wide variety of clinical manifestations: focal/multifocal chorioretinitis, acute posterior placoid chorioretinitis, necrotizing retinitis, retinal vasculitis, punctate inner retinitis, intermediate uveitis, and panuveitis.

Deep chorioretinitis used to be considered the most common form of posterior segment involvement. Focal syphilitic chorioretinitis presents as a deep, yellow gray lesion often with a shallow serous retinal detachment and inflammatory cells in the vitreous. Multifocal lesions from one half to one disk diameter can coalesce to become confluent. Fluorescein angiography shows a pattern of early hypofluorescence of the lesion followed by late staining.

Since the original description by Gass of a specific entity referred to as acute syphilitic posterior placoid chorioretinitis (ASPPC) in 6 patients with secondary syphilis, 16 similar cases are reported in the literature. These patients present with vitritis associated with large, solitary, placoid, pale-yellowish subretinal lesions usually in both eyes. The lesions show evidence of central fading and a pattern of coarsely stippled hyperpigmentation of the pigment epithelium. The placoid

lesions in ASPPC are larger in size and often solitary which differentiates them from thelesions observed in acute posterior multifocal placoid pigment epitheliopathy (AMPPE). The pattern of small leopard-spot alterations of the pigment epithelium seen on fluorescein angiography in the cicatricial phase of ASPPC is not seen in APMPPE and is sufficiently characteristic to suggest a diagnosis of syphilis according to Gass.

Necrotizing retinitis mimicking herpetic retinal necrosis has been reported in the recent literature with increasing frequency. This form of syphilitic retinitis presents as one or more yellow-white patches of necrosis, often associated with vasculitis, vitreous inflammation and discrete anterior segment inflammation, imitating closely the acute retinal necrosis syndrome (ARN) of herpetic origin. In the absence of adequate antibiotic therapy, the lesions will progress and cause serious visual disability in a matter of weeks. The tendency for bilateral disease and the more aggressive course observed in immunodeficient patients dictate the need for prompt diagnosis and effective treatment in this patient group. Although the differential diagnosis with ARN may be difficult, careful observation of the lesions may yield a clue to the diagnosis of syphilitic retinal necrosis. In ARN the necrotic lesions start in the periphery whereas in syphilitic retinitis they often are located in the posterior pole. In syphilitic retinal necrosis one has the impression that the surface of the lesion is somewhat indistinct, as if a layer of exudate obscures the underlying retina from view, whereas in ARN one can clearly identify the surface of the lesions as the surface of the thickened, necrotic retina. The retinal necrotic tissue tends to be homogeneous in ARN whereas the areas of necrosis in syphilitic retinitis have a mottled aspect that becomes even more obvious in the healing phase. The response to intravenous penicillin in syphilitic necrosis is excellent and halts further progression. The necrotic areas heal with scarring of the retinal pigment epithelium resulting in the picture of pseudo-retinits pigmentosa.

Recently, punctate retinitis with inner retinal and preretinal white dots was described as another typical presentation of syphilitic retinal involvement. The use of corticosteroids may contribute to the expression of this fundus pattern.

Syphilitic eye disease may mimic intermediate uveitis especially if mild inflammation of the anterior segment is associated with a more pronounced vitreal reaction. Other signs often present in intermediate uveitis such as retinal vasculitis, cystoid macular oedema and a hot disk may also be present, further confusing the observer. A frank pars plana exudate is not present in syphilitic vitreitis.

The reported prevalence of simultaneous involvement of the anterior and the posterior segment or panuveitis is highly variable and ranges from 27% to 66%.

Optic nerve inflammation

Acute meningitis occurs in 1% to 2% of patients with secondary syphilis and this can cause increased intracranial pressure and papilledema. In pure papilledema there is an enlargement of the blind spot but no signs of inflammatory cells in the vitreous. Papilledema should be

differentiated from inflammatory optic disk edema due to optic neuritis, papillitis, and neuroretinitis. These patients have marked loss of visual acuity and display central and cecocentral, or nerve fiber bundle defects, and often have signs of vitreous inflammation. In papillitis there is a swollen disk with intraretinal exudates and perivasculitis around it. When the inflammatory changes extend into the peripapillary retina resulting in hard exudates, the condition qualifies as neuroretinitis. Optic perineuritis is a distinct entity due to an inflammation of the meningeal sheaths of the optic nerve and causes mild swellling of the optic disk, without affecting its function. This condition should be suspected in patients with normal visual acuity and color vision who seem to have papilledema but in whom lumbar puncture reveals normal cerebrospinal fluid pressure and the presence of inflammatory cells or increased protein. Although inflammatory conditions of the optic nerve are more common in the secondary stage, they may occur in tertiary syphilis as well. Optic atrophy is however the prevailing pathology in this stage and is present in 5% of patients with symptomatic parenchymatous neurosyphilis.

Syphilitic uveitis in HIV infected patients

The prevalence of HIV infection and of syphilis is high in many countries of the developing world and coinfection with HIV and syphilis is common due to shared risk factors related to sexual behaviour. Syphilitic chancres like any genital ulceration increase the risk of acquiring and transmitting HIV. HIV infected patients with syphilis have a higher treponemal load and are more prone to develop neurosyphilis. Ophthalmic involvement in these patients is often bilateral and several reports suggests that syphilitic uveitis in HIV infected patients tends to run a more aggressive course and may relapse despite adequate treatment. Moreover, the serological diagnosis of syphilis is more challenging in HIV infected patients and depending on the stage of the disease, more false positive (early stage of HIV) or more false negative results (advanced immune dysfunction) may be encountered.

Diagnosis of ocular syphilis

Because of the wide variety of syphilitic ocular manifestations and the fact that this disease may mimick other etiologic entities, some practitioners routinely order serologic tests for syphilis in patients with intraocular inflammation. In populations of the industrialized world with a very low prevalence of syphilis, even in the selected population of uveitis patients, the rationale for this approach might be questioned. In low prevalence areas a more selective approach seems appropriate: testing for syphilis is indicated if the history or the presentation are suggestive; if the inflammation has unusual characteristics or if it fails to respond to the usual treatment (often steroids); or if the patient belongs to a high risk group for sexually transmitted diseases (HIV positive patients, men having sex with men, commercial sex workers). In those countries of the developing world where syphilis is rampant, it is probably justified to order syphilis serology on a routine base in any patient with intraocular inflammation that does not fit one of the well known (non syphilitic) uveitis entities.

Laboratory confirmation of syphilis can be obtained via direct detection of *Treponema pallidum* (darkfield microscopy, silver staining, direct fluorescent antibody stains) but this method is of

little use in ocular syphilis and often not available in the developing countries. Serologic testing that includes non-treponemal tests and treponemal tests is considered the standard detection method. The term non-treponemal is used because the antigens are not treponemal in origin, but are extracts of normal mammalian tissues. Cardiolipin from beef heart allows the detection of anti-lipid IgG and IgM formed in the patient in response to lipoidal material released from cells damaged by the infection, as well as to lipids in the surface of *T. pallidum*. The two tests commonly in use are theVDRL (Venereal Disease Research Lab) and the RPR (rapid plasma reagin). Non-treponemal antibody titers decline as a result of treatment. A fourfold reduction in antibody titer of the same non-treponemal test is considered a significant response to treatment Lack of expected reduction in titer or an increase in titer suggests treatment failure or reinfection. Non-treponemal tests may give false positive results in conditions other than syphilis (viral infection, pregnancy, post-immunization). Moreover, they may be negative in as many as 30% of patients during the late latent or tertiary stages. Due to the prozone phenomenon VDRL/RPR may be false negative on undiluted serum even in secondary syphilis, especially in HIV positive patients. Therefore, a specific treponema antibody assay is needed to supplement the non-treponemal tests in all cases of suspected disease. Two commonly used specific tests are the FTA-abs (fluorescent treponemal antibody absorption test) and the TP-PA (*T. pallidum* particle agglutination). These tests have a high sensitivity and specificity and are said to stay positive throughout life, although seroreversion may occur in a small number of patients, mainly in those treated for early disease. They are affordable and available even in most developing countries.

The CDC recommends lumbar puncture in all patients with ocular syphilis to detect neurosyphilis, but there is debate whether this procedure is justified in patients with isolated anterior segment inflammation. The diagnosis of neurosyphilis is based upon the cerebrospinal fluid leukocytosis, protein changes, and the presence of a positive VDRL. The VDRL test unfortunately has low sensitivity to detect syphilis in the cerebrospinal fluid and therefore a negative VDRL does not rule out neurosyphilis. Specific treponemal tests are not very useful to detect neurosyphilis because antitreponemal IgG antibodies pass the intact blood-brain barrier and hence a positive result is no proof of neurosyphilis. Therefore if one has the intention to administer the treatment for neurosyphilis to a patient with syphilitic ocular inflammation, lumbar puncture may not be necessary.

Treatment

Ocular syphilis is treated in exactly the same way as neurosyphilis. Since benzathine penicillin does not penetrate the blood ocular barrier, aqueous penicillin G or procaine penicillin G plus probenecid should be given. For patients with ocular syphilis in the tertiary stage a 3 week course of benzathine penicillin should be added.

Stage	Patients not allergic to penicillin	Patients allergic to penicillin
Neurosyphilis (any stage)	Aqueous crystalline penicillin G 3-4 million units IV every 4h or 18-24 million units/day for 10-14 days or Procaine penicillin 2.4 million units IM once daily plus probenecid 500 mg PO 4 times daily for 10-14 days	Ceftriaxone 2g IV or IM daily for 10-14 days
Neurosyphilis (late stage)	Above regimen followed by benzathine penicillin G 2.4 million units IM every week for up to 3 weeks	

Antibiotic therapy is essential in infectious uveitis, but there is certainly a place for adjunctive corticosteroid therapy in the management of syphilitic eye disease. Topical steroids are of benefit as an adjunctive treatment in syphilitis keratitis, scleritis and anterior uveitis. Systemic steroids always in combination with appropriate antibiotic therapy have a role in the treatment of posterior uveitis and optic nerve inflammation.

Pinta, also known as *mal de pinto*, *enfermedad azul, carate* and *cute*, is the mildest of the endemic treponematoses and the lesions are strictly confined to the skin. The disease remains endemic in remote regions of Mexico and of Central and South America (the Amazone region of Brazil). There is no systemic involvement.

Diagnosis of endemic treponematoses

The presumptive diagnosis of yaws, endemic syphilis, or pinta should be based on a careful clinical examination with a full knowledge of the local epidemiological context. Few health care workers however have the necessary skills to diagnose these diseases especially when confronted with sporadic cases outside areas of endemicity. The differential diagnosis with other dermatological conditions may be notoriously difficult. Radiology of the bones can aid in the diagnosis of yaws and endemic syphilis, but is often not at hand in remote rural areas. Dark field microscopy of the serous exudate of lesions allows an instant diagnosis of treponematoses, but requires a well-trained and experienced observer. Direct fluorescent antibody test is more sensitive and

specific than dark field microscopy, but this technique is only available in reference centers. The serological tests for treponematoses are affordable and readily available. They are particularly useful to confirm a reactive non-treponemal test (exclusion of false positives). Non-treponemal tests are helpful in the follow up after treatment: a fourfold decrease in antibody titers indicates successful treatment whereas a fourfold increase suggests re-infection or relapse. It should be repeated however that at present no serological test is able to distinguish between venereal and endemic syphilis. Mistaking endemic treponematoses for venereal syphilis should be avoided given the serious social implications.

Conclusion

Ocular syphilis, probably more frequent in patients with HIV co-infection, causes a wide variety of ocular inflammatory conditions and only a few of them are pathognomonic for the disease. Therefore, the ophthalmologist must maintain a high degree of suspicion for syphilis especially in patients with ocular inflammation of unknown etiology, in patients who fail to respond to or worsen on immunosuppressive therapy, or in patients in whom the natural course of the disease does not follow the pattern predicted by the presumed etiology. Prompt diagnosis is particularly important in patients with syphilis and HIV co-infection, since aggressive, bilateral necrotizing syphilitic retinitis emerges as a potentially blinding disease in this patient group. Finally, since many patients with syphilitic uveitis present in the secondary stage, timely diagnosis and adequate treatment will prevent not only further ocular damage, but will also protect the patient against morbidity and even mortality associated with the tertiary stage of the disease.

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TUBERCULOUS UVEITIS

Introduction

Tuberculosis (TB) is a slowly progressive, chronic, granulomatous infection caused by the acid-fast bacillus *Mycobacterium tuberculosis*. This germ has a predilection for the lungs but almost any organ or tissue can be affected, including the eye.

According to WHO data, about one third of the world ‘s population is infected with TB and it is estimated that 80% of the total burden of TB is concentrated in the developing world, where poor hygiene, crowding, malnourishment and high prevalence of HIV are common risk factors. The HIV epidemic goes hand in hand with a recrudescence of TB for the following reasons: HIV is a risk factor for the development of active TB and patients with active TB have higher viral loads and faster progression of disease compared to HIV-infected patients without TB. TB is now second only to HIV as the cause of adult death in developing countries.

Epidemiology of tuberculous uveitis

The diagnosis of tuberculous uveitis is by no means easy and epidemiological data for tuberculous uveitis are not very reliable. In the first half of the previous century, some authors considered tuberculous uveitis to be a very common disease and Guyton and Woods for example estimated that 80% of granulomatous uveitis was caused by TB in 1940. At present, tuberculous uveitis is considered to be rare in the industrialized world. In India where the disease is endemic, TB is considered to play a role in 5% to 10% of all uveitis cases. Similar figures were obtained from Japan and Saudi-Arabia.

Clinical features

Intraocular TB can be the result of direct infection (granulomas of the iris and/or choroid; abscesses; endophthalmitis; panophthalmitis) or it can be induced by an immune-mediated hypersensitivity response (retinal vasculitis, serpiginous choroiditis). These diverse manifestations of the disease make it a mimicker of other conditions.

The prototype of direct infection are choroidal tubercles and tuberculomas (large, solitary masses) as a result of hematogenous seeding to the choroid. The differential diagnosis includes sarcoid granulomata, syphilitic graulomata and metastatic lesions. There is often an overlying exudative retinal detachment. An example of the indirect immune-mediated type of lesion is the multifocal, slowly progressive choroiditis with extension from an active edge in an amoeboid pattern, strongly resembling idiopathic serpiginous choroiditis.

Tuberculous retinal vasculitis presents as an active retinal periphlebitiswith thick exudates around the veins. It is associated with retinal hemorrhages and infarction, leading to ischemia, proliferative retinopathy, recurrent vitreous hemorrhages , traction retinal detachment, rubeosis iridis and neovascular glaucoma.

Diagnosis

The diagnosis of tuberculous uveitis may be exceedingly difficult as most patients with ocular involvement have no history of pulmonary or systemic TB. Indeed, about 60% of patients with extrapulmonary TB have no evidence of pulmonary TB.

The definite diagnosis of tuberculous uveitis can only be established when M tuberculosis is isolated from the eye (culture or demonstration of acid fast bacilli). In most cases it is difficult to obtain intraocular specimens and the culture takes several weeks. PCR is not yet implemented as a routine procedure. Therefore, most of the time the diagnosis of tuberculous uveitis will be a diagnosis of presumed ocular tuberculosis. In many studies the criteria for presumed ocular tuberculosis include the following:

1. Ocular findings consistent with possible intraocular TB after exclusion of other causes of uveitis

2. Strongly positive tuberculin skin test

3. Response to antituberculous therapy with absence of recurrences

Tuberculin skin test

= intradermal injection of 5 tuberculin units

Induration is read after 48 to 72 hours:

< 5 mm: negative

5 to 10 mm: considered positive in HIV patients, immunosuppressed patients, in those who are in close contact with active TB patients, and in those showing healed TB lesions on chest X-ray

> than 10 mm: considered positive in health care workers and in people living in highly endemic areas

> 15 mm: considered positive in all patients

However, many conditions are associated with false negative answers: advanced TB, immune suppression, sarcoidosis, aging, steroid use, viral illnesses. Note that the effect of vaccination with BCG declines over time and that a positive TST of 15 mm or more is unlikely to be due to vaccination.

Radiology

Chest X-ray and especially CT scan are useful to detect lung involvement and mediastinal lymphadenopathy.

Interferon-gamma release assays

These tests detect TB infection by measuring in vitro T-cell interferon-gamma release in response to antigens that are highly specific for M tuberculosis but absent from the BCG vaccine. The place of these new tests in the clinical setting is not yet clear.

Molecular techniques

Traditional culture techniques for M tuberculosis on Loewenstein-Jenson media require several weeks to 2 months and are not suited for detection of TB in ocular samples (small amounts and low bacterial yield). Therefore, PCR techniques to detect TB bacterial DNA in clinical specimens from the eye (aqueous humour, vitreous samples, etc.) would be a big advantage.

Treatment of ocular TB

The treatment of ocular TB should be directed against the infectious disease and against the deleterious immune response in the eye. Therefore, a combination of antituberculous treatment (isoniazid, rifampicin, ethambutol, pyrazinamide) and systemic steroids is recommended. Since these drugs are toxic, the treatment should be supervised by an infectious disease specialist. The management of ischemic retinal disease may require panretinal photocoagulation and even vitrectomy and endolaser for recurrent hemorrhages and fibrovascular proliferation.

Take home messages:

Reemergence of TB (especially in HIV + patients)

Patients with extrapulmonary (eye!) disease: often no sign of lung disease

Treatable disease, but difficult diagnosis (high index of suspicion mandatory)

Treatment = anti-TB + systemic steroids + treatment of complications (e.g. laser)

Resolution of inflammation and absence of recurrences = confirmation of “presumed” ocular TB

Philippe Kestelyn
Ghent University Hospital
Dept. Ophthalmology
De Pintelaan 185
9000 Gent
Belgium

The widening spectrum of herpetic retinopathies

Bahram BODAGHI, MD, PhD
Dept of Ophthalmology
University of Paris VI,
Pitié-Salpêtrière Hospital, France

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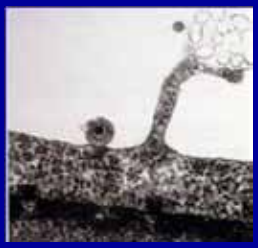
Introduction

- Major infectious entity
- Absolute emergency situation in uveitis
- High rate of complications
- Poor visual outcome



Kirisawa's uveitis

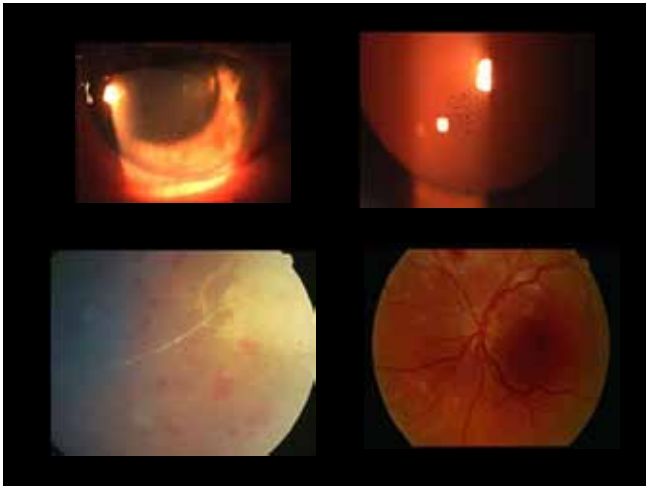
(*Urayama et al.* 1971)

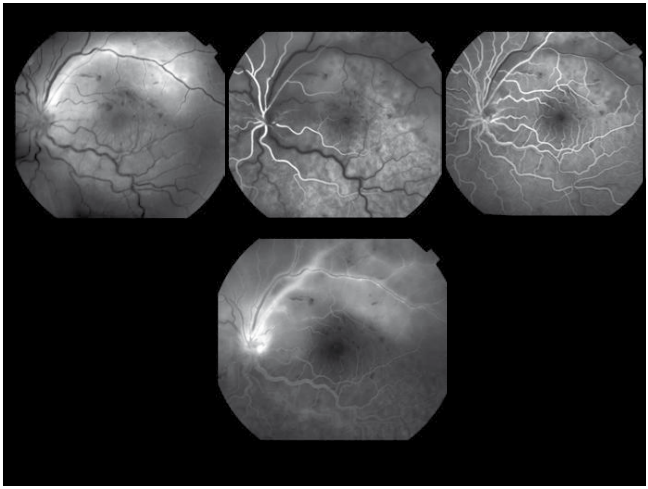
- Acute uveitis
- Retinal obliterative vasculitis
- Confluent yellow-white lesions
- Retinal periphery

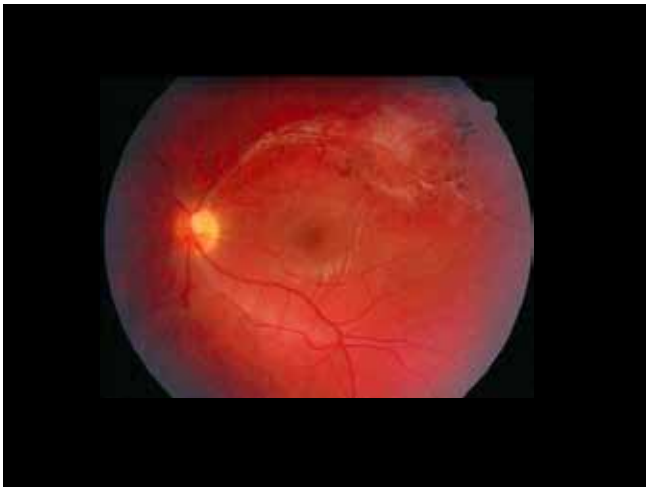
ARN syndrome

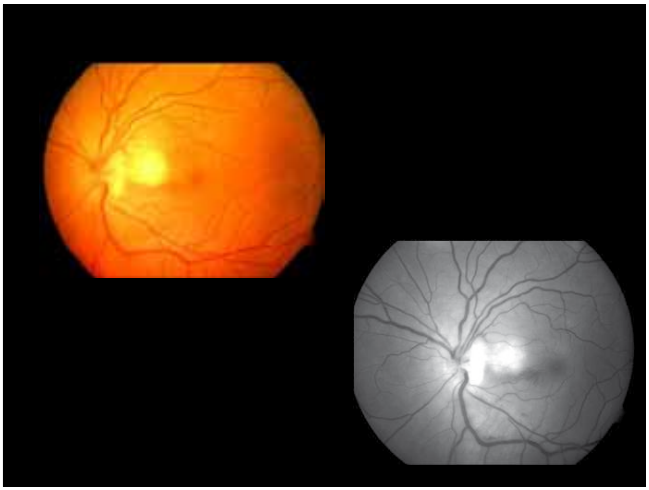
- Focal, peripheral well-demarcated areas of retinal necrosis
- Rapid and circumferential progression
- Vitritis+++ and AAU
- Occlusive vasculopathy
- IC or IS patients

- ~500 reported cases (all ages)
- Bilateral in 1/3 (1-4 months)
- Recurrences are rare in the same eye









Viral retinitis after intravitreal steroid administration

- Retrospective, observational case series.
- 736 intravitreal triamcinolone (IVTA) between September 2002 and November 2008
- Viral retinitis in 3 patients (overall incidence of 3 in 736 or 0.41%)
- 334 injections in patients with an immune-altering condition, including diabetes
- All 3 of the patients in whom viral retinitis developed after IVTA injection possessed abnormal immune systems (overall incidence of 3 in 334 or 0.90%)

Shah AM et al. Am J Ophthalmol. 2010

Viral causes of ARN

PCR analysis from AH+V

- 28/29 ARN+
- HSV-1 = 7 (25%)
- HSV-2 = 6 (21,4%)
- VZV = 13 (46,4%)
- CMV = 1 (3,6%)
- Mean age
  - **HSV-2 group < 25 years**
  - **HSV-1 group = 47 years**
  - **VZV group = 57years**

Ganatra JB, Am J Ophthalmol, 2000

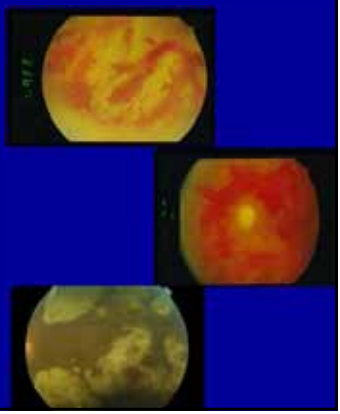
PCR analysis from AH

- 19/22 +
- ARN group = 19 patients
  - **HSV-1 = 2 (10.5%)**
  - **HSV-2 = 4 (21.1%)**
  - **VZV = 6 (31.6%)**
  - **CMV = 4 (21%)**
  - **EBV = 1 (5.2%)**
- PRN group = 3 patients
  - **VZV = 3/3**

Tran, Br J Ophthalmol, 2003

RPORN syndrome

- *Forster et al. 1990*
- IS patients +++
- Full thickness retinal necrosis in the posterior pole, the midretina and the peripheral retina
- Retinitis progressively spreads outwardly and peripherally, often becoming confluent
- Multiple areas of various sizes
- Minimal vitritis and non granulomatous mild AU
- Bilateral in 71% of cases, vasculitis and optic neuritis (rare)
- Visual prognosis : guarded+++



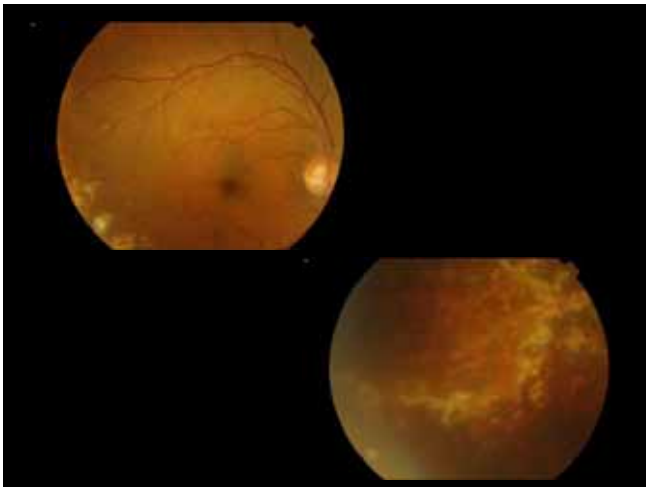
HAART era

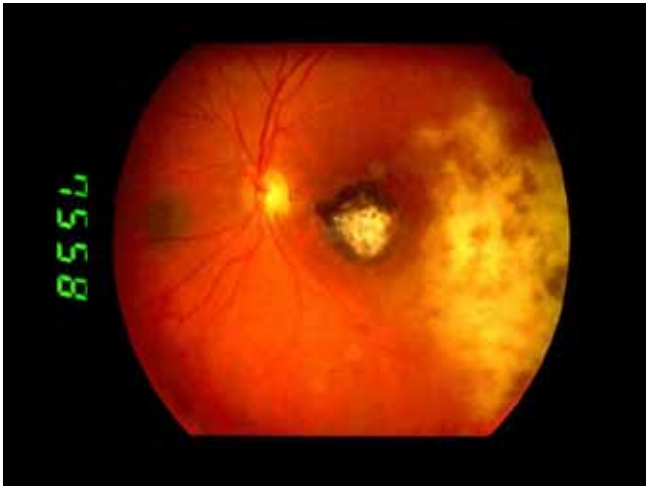
- Incidence of CMV retinitis : 5.6/100 PY (most in HAART-failure patients)
- IRU : response to CMV antigens
- Incidence 0.1-0.8 PY of follow-up
- Similar pattern in patients with previous ocular toxoplasmosis and TB

Holland, Am J Ophthalmol, 2008

Jabs, Arch Ophthalmol, 2008

Otiti-Sengeri et al. Curr Opin HIV AIDS, 2008

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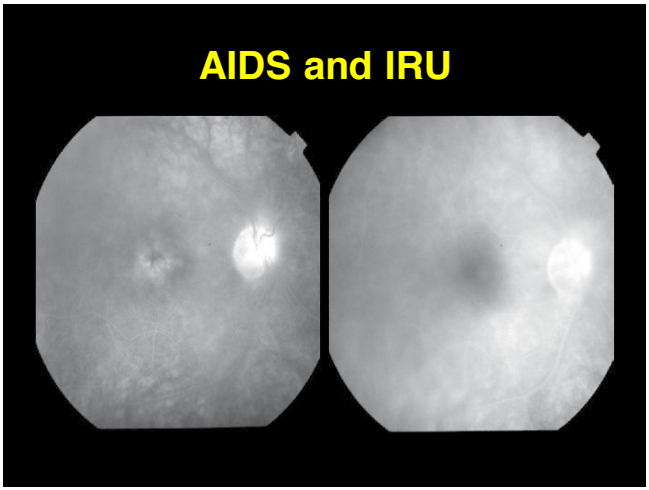
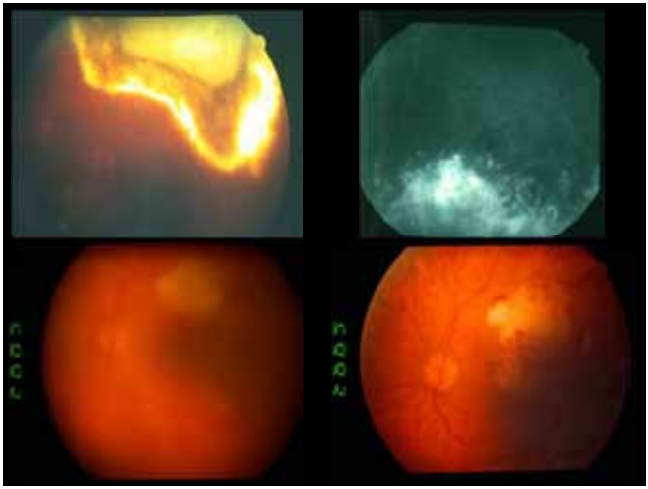


Differential Dx


Moshfeghi et al. 2004 Ophthalmology
Balansard et al. 2005 Br J Ophthalmol



PCR

- Conventional PCR
- Real time PCR+++ → Rapidity; High sensitivity; Quantification
- Multiplex PCR
- Nested-PCR

Lightcycler

ABI PRISM 7000

Dworkin et al. Arch Ophthalmol, 2002
Rothova et al. Ophthalmology, 2008

Usual Treatment

Emergency +++

- **intravenous** acyclovir **: 10mg/kg x 3/day**
  (ACV) for 10 days

- **followed by oral** valacyclovir **: 1g x 3/day**
  (val ACV) for 6 weeks

Acute Retinal Necrosis (Pitie-Salpetriere)

- Induction Rx with antiviral agents :
  - **. i.v. acyclovir (10 mg/kg/8h)**
  - **. i.v. ganciclovir (5 mg/kg/12h) ++**
  - **. i.v. foscarnet (90 mg/kg/12h) +++**
- Maintenance Rx :
  - **. oral valacyclovir (3g/d) +++**
  - **. oral valganciclovir (900 mg/d)++**
- Intravitreal injections : optional
  - **. ganciclovir :200-2000 microg x 2 per wk +++**
  - **. foscarnet : 1200 microg x 2 per wk**
- Duration ? 3 months to x years

ARN (Treatment)

- Use of steroids = controversial, only after initiation of antiviral Rx
  - **. oral prednisone : 0.5-1mg/kg/day;**
  - **. rarely, i.v. methylprednisolone**

- Never use immunosuppressive agents +++
- Anticoagulation (heparin, aspirin)
- Laser photocoagulation :
  - **. unable in halting the spread of the retinitis**
  - **. may prevent RD**

-Prophylactic vitrectomy : controversial

Kawaguchi T et al. Semin Ophthalmol, 2008
Hillenkamp J et al. Ophthalmology, 2009

ACV vs newer antiviral therapies

- Multicenter, nonrandomized, retrospective, interventional series
- 58 patients diagnosed with ARN by a retina specialist at 1 of 4 referral centers between 1981 and 2008
- Cohort divided into 2 subgroups:
- Rx during the ACV-only era (n = 36) and Rx during the current era of newer antiviral medications (n = 22)
- iv, oral, or IVT antivirals (ACV, valACV, FCV, valGCV, GCV, FCN and prophylactic laser retinopexy, aspirin; oral steroids
- Main outcome measures : VA, RD, and fellow eye involvement

Results

- Wide range and combination of antiviral agents currently used for initial and long-term treatment of ARN
- Outcomes from the newer antivirals era were similar to those achieved during the ACV-only era. In both groups, the incidence of 20/200 or worse visual acuity was 24% per person-year (P = 0.91).
- The prevalence of retinal detachment : 50% in each group (P = 0.59). No variables, including prophylactic laser retinopexy, were associated with risk of retinal detachment.
- 2 patients (3.4%) developed ARN in the initially unaffected eye

Tibbetts MD et al. Ophthalmology 2010

Severity and virus type

- Retrospective comparative case series
- 81 eyes of 74 patients
- IVT Foascarnet + systemic Rx
- Evolution of VA and progression to RD
- 33 HSV and 48 VZV
- Poor prognosis in the VZV group (importance of viral identification)
- RD : 2.5X more common in the VZV group
- Less RD in the group with IVT Foscarnet

Wong et al. Ophthalmology, 2010

Long-term follow-up

Retrospective

32 patients (from 1998 to 2007)

IVT GCVand/or FCN : 11/25 eyes

iv and oral antivirals : 14/20 and 19/20 patients

Better outcome if less than 25% of the retina is involved

No RD in 6 eyes treated with prophylactic laser

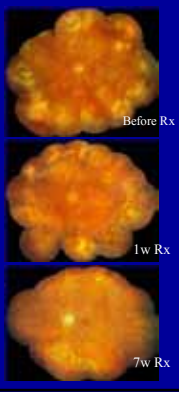
Meghpara B et al. 2010

Primary Treatment of Acute Retinal Necrosis with Oral Antiviral Therapy

Therapeutic alternative

- Retrospective, uncontrolled, interventional case series
- 8 consecutive patients with newly diagnosed ARN treated solely with oral antiviral medications
- Resolution of ARN : 100%
- Initial response to Rx : 4 d (5 eyes), median time to complete resolution of 14 d
- Final VA : improved (6); stable (2); worse (2)
- Follow-up : 36 weeks (7-72 w)
- RD : 3 cases

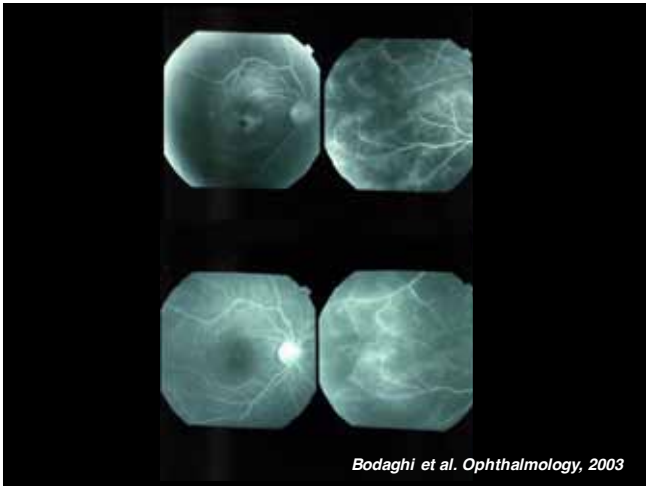
Aizman et al. Ophthalmology, 2007



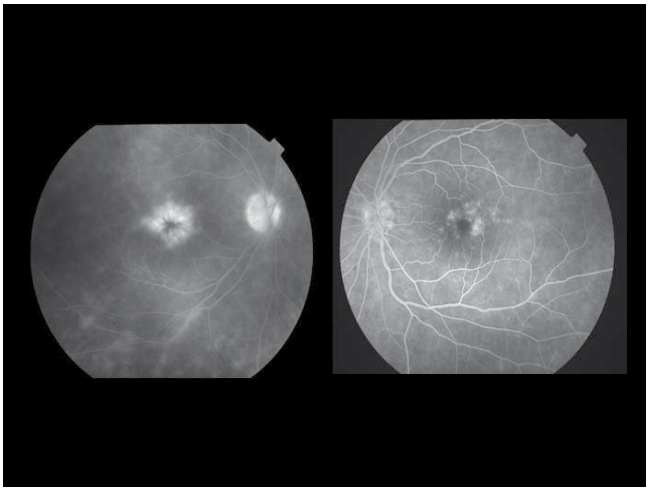
Emerging entities

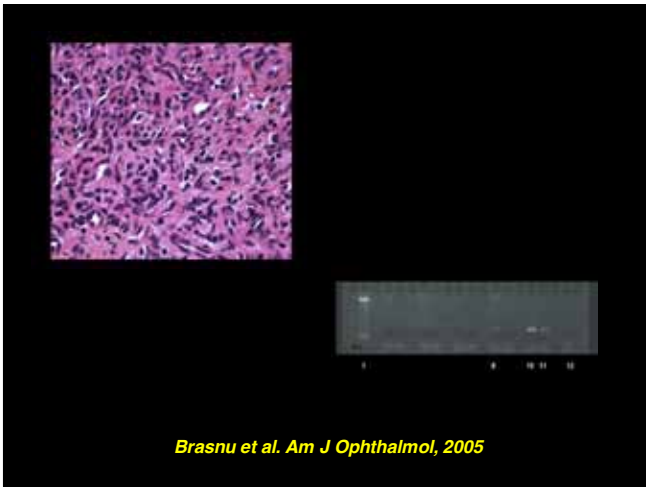
To identify viral agents, especially herpes-viruses, in atypical presentations of intraocular inflammation

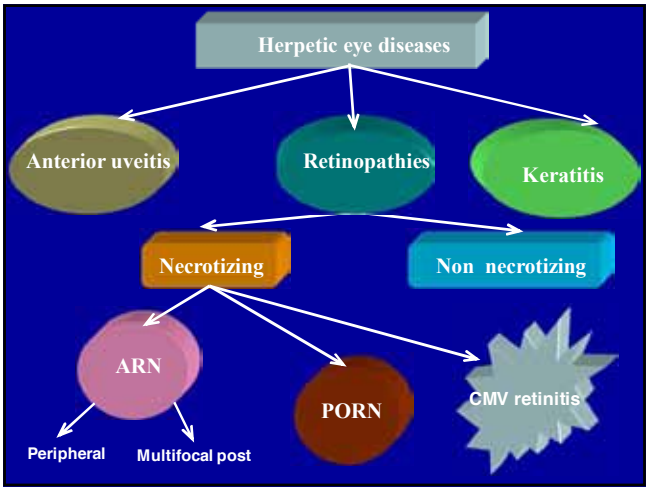
Nonnecrotizing Herpetic Retinopathies: Masquerading as Severe Posterior Uveitis



Bodaghi et al. Ophthalmology, 2003




Brasnu et al. Am J Ophthalmol, 2005



Conclusions

- Absolute emergency
- Sight-threatening despite appropriate Rx
- Different entities with similar clinical presentations
- Importance of virological Dx confirmation
- Therapeutic approach adapted to the severity of each case and initiated without delay

Notes

European Vision Eye Research

Crete

Oct 5-8, 2011

www.ever.be

The 11th International Ocular Inflammation Society Congress and International Assembly of Ocular Inflammation Societies

Organized by the International Ocular Inflammation Society in conjunction with Uveitis Society of India, local organizing society

Goa, India
November 13-16, 2011

Participating organizations: International Uveitis Study Group; American Uveitis Society
Asia Pacific Intraocular Inflammation Study Group
Society for Ophthalmo-Immuninfectiology in Europe
Sociedad Panamericana de Enfermedades Inflamatorias Oculares
International Ocular Sarcoidosis Study Group
International VKH Disease and Sympathetic Ophthalmia Study Group
International Ocular Behcet's disease Study Group;
International Ocular Tuberculosis Study Group
Foster Ocular Immunology Society
Chinese Uveitis Society; Hellenic Uveitis Society; Portuguese Uveitis Society

Bahram BODAGHI, MD, PhD
Dept of Ophthalmology
University of Paris VI,
Pitié-Salpêtrière Hospital, France

Notes

Lymphoma and masquerade

Phuc LeHoang, France

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MASQUERADE SYNDROMES

DEFINITION

Masquerade syndromes comprise a group of disorders

- simulating a chronic idiopathic uveitis
- having an underlying primary cause that is not immune mediated and that is associated with an apparent clinical picture of intraocular inflammation

They are usually poorly, if not at all, responsive to corticosteroid treatment.

One must be suspicious when the apparent intraocular inflammation :

- is unilateral
- occurs either in very young children or in the elderly

DIFFERENTIAL DIAGNOSIS

Masquerade syndromes can simulate intraocular inflammation caused by :

- sarcoidosis
- tuberculosis
- syphilis
- toxoplasmosis
- toxocariasis
- ARN
- Whipple's syndrome
- intermediate uveitis, pars planitis
- idiopathic vasculitis
- birdshot retinochoroidopathy
- idiopathic scleritis

CLASSIFICATIONS

The main disorders that can masquerade as an uveitis are intraocular tumors, postoperative infections or degenerative conditions.

Several classifications can be suggested to facilitate the practical approach to the diagnosis of these masquerade syndromes.

1/ Malignant and non-malignant disorders

2/ Diagnostic directions according to the patient's age

3/ Anatomical classification (anterior, intermediate, posterior)

Because of an important impact on the life-expectancy of the patients, we will focus on the malignant disorders that can masquerade as an uveitis and need to be early diagnosed for an early treatment.

MALIGNANT AND NON-MALIGNANT DISORDERS

This classification is the first to consider by the practitioner to avoid serious misdiagnosis and mismanagement of an apparent uveitis.

The family history, the past medical history, the ocular history, the review of systemic complaints, the general physical examination, the direct ocular examination, the clinical course and the response to treatment should always be considered to rule out not only infectious etiologies (that can respond to specific treatment) but also any malignant disorders that can cause an apparent intraocular inflammation.

Diagnostic tests may help to recognize the different masquerade syndromes ; they are easy and logical to indicate when the cause of the pseudo-uveitis is called to mind.

1. Malignant disorders

1.1. Malignant disorders in adults

1.1.1. Intraocular lymphoma

a) Primary ocular-CNS non Hodgkin's lymphoma

- Large B cell lymphoma
- Increased incidence
- Elderly patients
- Bilateral most of the time
- Ocular involvement may precede detectable lesions in other parts of the CNS
- Blurred vision and floaters with non painful and white eyes
- Minimal or no anterior segment inflammation
- Sheets of vitreous cells, subretinal infiltrates, vasculitis
- Poorly responsive to corticosteroid treatment

→ Diagnosis :
- fluorescein angiography (leopard appearance), MRI
- elevated IL-10 levels in aqueous humor, vitreous, CSF
- cytologic examination of the AH, the vitreous and the CSF
- immunohistochemical staining for B and T cell markers and for kappa and lambda light chains
- detection of immunoglobulin gene rearrangement and translocation (combination of microdissection and PCR techniques)
- Differential diagnosis : lymphoid hyperplasia of the uvea
- Atypical presentations : acute optic neuropathy in the absence of any infiltration of the posterior segment, mild auto-immune-like uveitis and epilepsy, tuberculosis-like uveitis, acute retinal necrosis like presentation.

→ Treatment : systemic and intrathecal chemotherapy ± radiotherapy intravitreal chemotherapy

b) Systemic non-Hodgkin's lymphoma metastatic to the eye

- infiltration of the choroid
- hypopion or hyphema in an uninflammed eye

1.1.2. Uveal malignant melanoma simulating scleritis, anterior uveitis or choroidal granuloma.

- FA, ICG, ultrasonography, fine-needle aspiration

1.1.3. Metastatic tumors

- renal, lung and breast carcinomas
- cutaneous malignant melanoma
- leukemia
- Waldenstrom's disease

1.1.4. Paraneoplastic syndromes (Cancer-associated retinopathy, Bilateral diffuse uveal melanocytic proliferation) ; bilateral most of the time serum anti-recoverin antibodies, diagnosis of the primary tumor

1.2. Malignant disorders in childhood

1.2.1. Retinoblastoma (usually before the age of 5 years)

- inflammatory signs
- pseudo-hypopion in very large retinoblastomas or in diffuse infiltrating retinoblastomas ; the later can occur after 5 years of age, as old as 12 years.
- calcifications (ultrasonography, CT scan)
- anterior chamber tap = dangerous (lactic deshydrogenase, enolase, rosette forming cells)
- vitrectomy contraindicated
- sometimes difficult to differentiate from ocular toxocariasis

1.2.2. Leukemia

- acute myelomonocytic leukemia
- acute lymphocytic leukemia (possible intraocular recurrence)

2. Non-malignant disorders

- Intraocular foreign body
- Irido-corneo-endothelial syndrome (ICE)
- Drug associated uveitis (rifabutin, cidofovir)
- Pigment dispersion syndrome, pigmentary glaucoma (bilateral most of the time)
- Heterochromic Fuch's cyclitis
- Anterior segment ischemia (carotid artery disease, irradiation, extraocular muscle disinsertion)
- Amyloidosis (bilateral most of the time)
- Peripheral retinal detachment (inflammatory reaction, tobacco dust)
- Myelinated nerve fibers
- Old vitreous haemorrhage
- Retinal degeneration, retinitis pigmentosa (bilateral most of the time)
- Best's disease, fundus flavimaculatus (bilateral most of the time)
- Central serous choroidopathy
- Complications of severe systemic hypertension (choroidal ischemia)
- Endogenous endophthalmitis
- Myopic degeneration, paving stone degeneration
- Coat's disease

- In childhood : Juvenile xanthogranuloma (skin or iris biopy)
  Persistent hyperplastic primary vitreous

- In the elderly : Postoperative infections (cataract surgery) :
  fungal, P. acnes, Staphylococcus epidermidis

DIAGNOSTIC DIRECTIONS ACCORDING TO THE PATIENT'S AGE

(The following classification is only indicative : there are exceptions to the rule).

1. Under 15 years

- Retinoblastoma
- Acute leukemia
- Medulloepithelioma
- Juvenile xanthogranuloma (skin or iris biopy)
- Persistent hyperplastic primary vitreous

2. Adult

20 + years

- Drug associated uveitis (rifabutin, cidofovir)
- Pigment dispersion syndrome, pigmentary glaucoma (bilateral most of the time)
- Irido-corneo-endothelial syndrome (ICE)
- Acute leukemia
- Systemic lymphoma
- Hodgkin's lymphoma
- Coat's disease
- Amyloidosis (bilateral most of the time)

50 + years

- Chronic leukemia
- Metastatic solid tumors
- Uveal malignant melanoma
- Paraneoplastic syndromes (Cancer-associated retinopathy, Bilateral diffuse uveal
- melanocytic proliferation) (bilateral most of the time)
- serum anti-recoverin antibodies, diagnosis of the primary tumor
- Waldenstrom's disease

60 + years

- Primary ocular-CNS non Hodgkin's lymphoma (bilateral most of the time)
- Postoperative infections (cataract surgery) : fungal, P. acnes, Staph. Epidermidis.

3. Any age

- Intraocular foreign body
- Anterior segment ischemia (carotid artery disease, irradiation, extraocular muscle disinsertion)
- Peripheral retinal detachment (inflammatory reaction, tobacco dust)
- Retinal degeneration, retinitis pigmentosa (bilateral most of the time)
- Old vitreous haemorrhage
- Heterochromic Fuch's cyclitis
- Endogenous endophthalmitis

ANATOMICAL CLASSIFICATION

1. Anterior pseudo-uveitis

- Retinoblastoma
- Metastatic tumors (carcinoma, systemic lymphoma, leukemia …)
- Iris melanoma
- Primary ocular-CNS non Hodgkin's lymphoma (bilateral most of the time)

- Juvenile xanthogranuloma (skin or iris biopy)
- acanthamoeba
- ICE
- Intraocular foreign body
- Amyloidosis (scalloped pupils) (bilateral most of the time)
- Pigment dispersion syndrome, pigmentary glaucoma (bilateral most of the time)
- Heterochromic Fuch's cyclitis
- Anterior segment ischemia (carotid artery disease, irradiation, extraocular muscle disinsertion)
- Causes of pseudo-anterior uveitis with possible hypopion :
    - Retinoblastoma
    - Leukemia
    - Primary ocular-CNS non Hodgkin's lymphoma
    - Systemic lymphoma
    - Secondary infection to undiagnosed intraocular foreign body
    - Postoperative infections : fungal, P. acnes
    - Endogenous endophthalmitis
    - Drug-induced uveitis

2. Pseudo-vitritis

- Primary ocular-CNS non Hodgkin's lymphoma (bilateral most of the time)
- Intravitreal metastasis (carcinoma, leukemia, Waldenstrom's disease …)
- Retinoblastoma
- Postoperative infections : fungal, P. acnes
- Old vitreous haemorrhage
- Amyloidosis (bilateral most of the time)
- Heterochromic Fuch's cyclitis
- Persistent hyperplastic primary vitreous
- Endogenous endophthalmitis

3. Pseudo-posterior uveitis

- Retinoblastoma
- Metastatic tumors (carcinoma, systemic lymphoma, leukemia …)
- Uveal malignant melanoma
- Primary ocular-CNS non Hodgkin's lymphoma (bilateral most of the time)
- Paraneoplastic syndromes (Cancer-associated retinopathy, Bilateral diffuse uveal melanocytic proliferation) (bilateral most of the time) serum anti-recoverin antibodies, diagnosis of the primary tumor
- Intraocular foreign body
- Peripheral retinal detachment
- Retinal degeneration, retinitis pigmentosa (bilateral most of the time)

Cross-checking these non exhaustive lists according to the age of the patient, to the location and to the type of the apparent intraocular inflammation can help to draw up several hypotheses in the presence of an chronic uveitis unresponsive to conventional therapy. In fact, for every uveitis patient, this approach must be systematically used even before asking for laboratory tests and before giving any treatment. This is particularly true for unilateral uveitis or for uveitis occurring either in early childhood or in the elderly.

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Phuc LEHOANG, MD, PhD
Professor of Ophthalmology, Universite Pierre et Marie Curie
University Hospital La Pitié-Salpêtrière
83 Boulevard de l'Hôpital, 75013 Paris, France

Retinal vasculitis: general considerations and differential diagnosis

Manfred Zierhut, Germany

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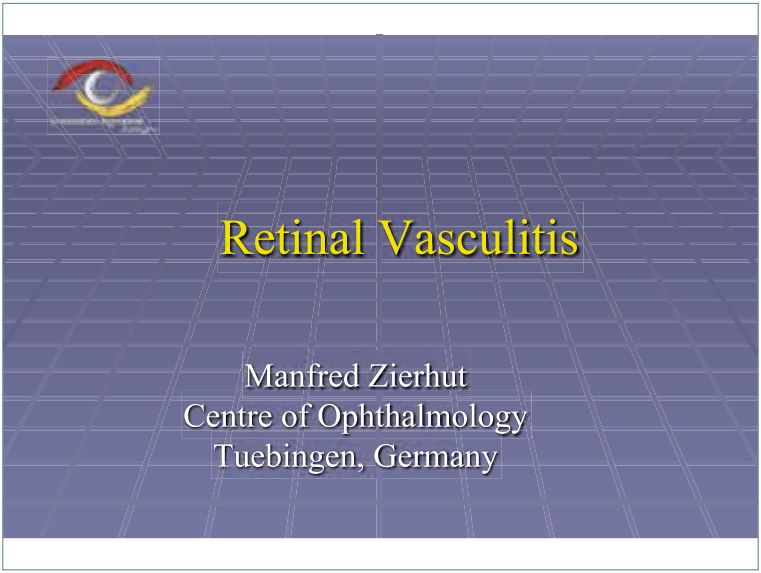
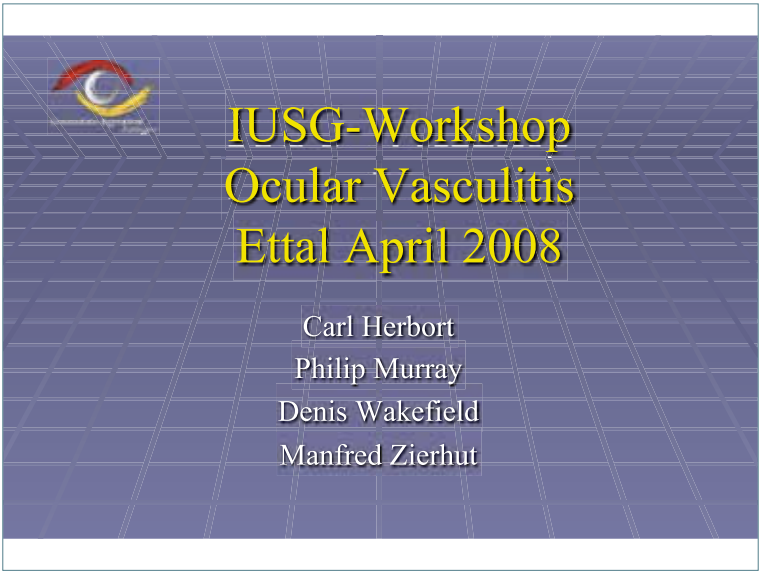
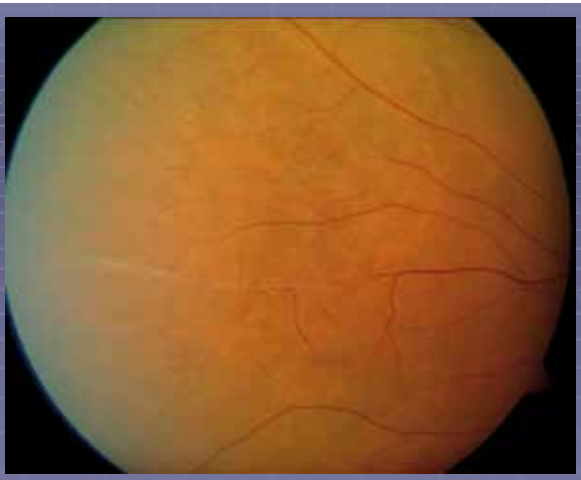




Idea for this Workshop

- Standardization of Uveitis Nomenclature (SUN)
- Various clinical situations
  - Diagnostic terminology
  - Inflammation grading schema
  - Outcome measures
- Vasculitis ???



Ettal Workshop

- Participants
  - 36
  - 11 countries
  - rheumatology, internal medicine, immunology, epidemiology

Why do we need a nomenclature for retinal Vasculitis?

- Imagine a patient
- picture fits to "vasculitis"
- you have to follow him for the next years
- communication better with nomenclature
  - for control
  - to qualify him for a study

The Optimal Way

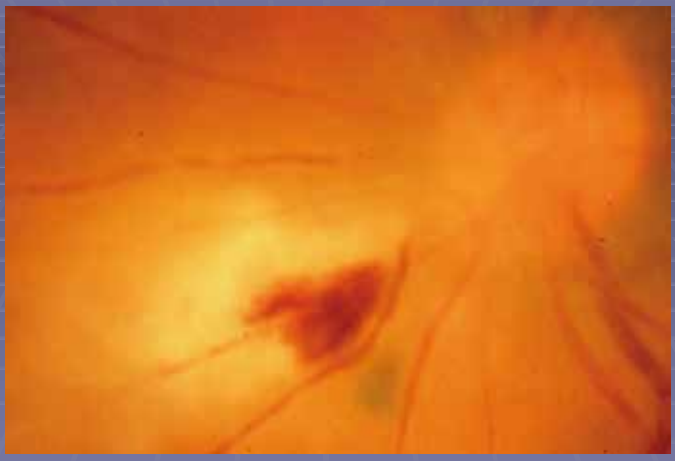
- What is "Ocular vasculitis"?
  - Interdisciplinary approach
  - Nomenclature of ocular vasculitis (descriptive) with validation
  - Severity Scoring System
  - Definition

Involved Eye

- OD
- OS
- OU

Association to other disorders

- Primary ocular vasculitis
  (vasculitis limited to the eye): I
- Secondary ocular vasculitis
  (eye involvement in systemic vasculitis): II



The type of vessel involved

- A: Arterial vessels
- V: Venous vessels
- C: Capillaries

Ettal 2008

- What is "Ocular vasculitis"?
  - limit to: retinal Vasculitis
- Nomenclature of ocular vasculitis
  - collection of terms

Descriptive Terms for Retinal Vasculitis

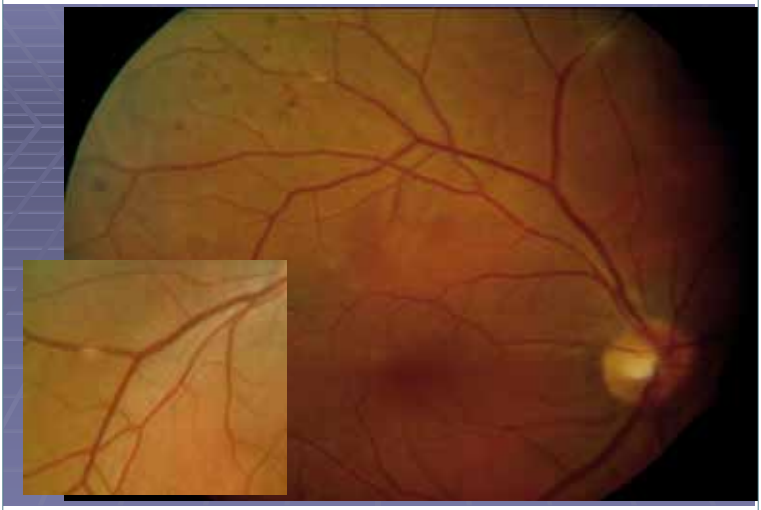
- based on signs of vasculitis
- clinically, not histologically, should include all biomarkers available and angiography
- proposals were only accepted with 75% voters

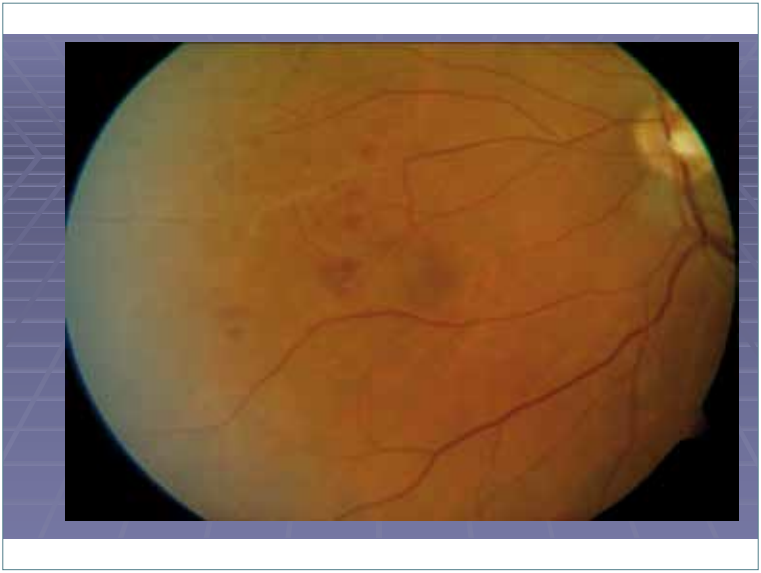
Retinal Vasculitis Terms

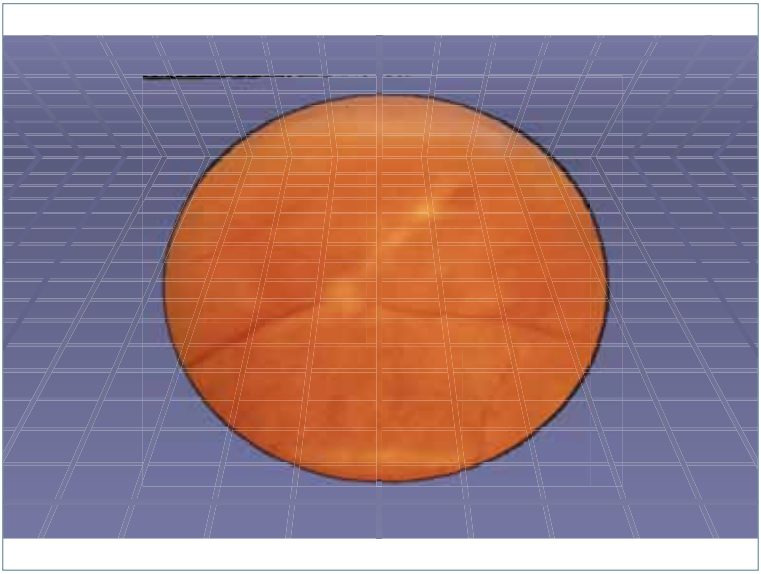
- **32 terms have been accepted by voting**
- **importance**
- **association to ret. vasculitis**
- **typical but not mandatory and not exclusive**
- **terms associated to activity or complications**

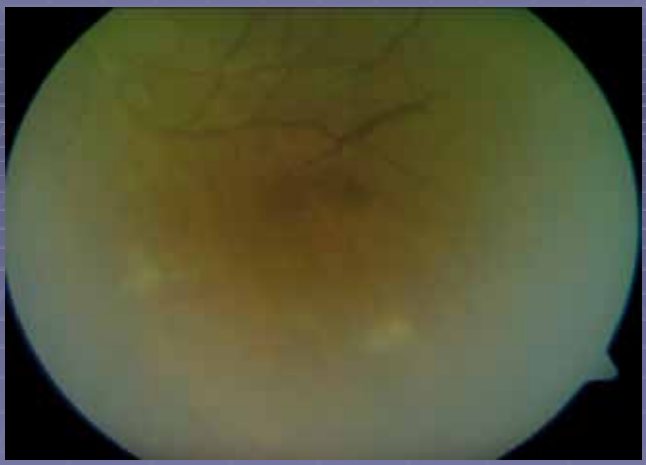
Examples for Retinal Changes

- ischemic signs
  - cotton wool spots, retinal infarction,
  - areas of non-perfusion,
  - neovascularization,
- postinflammation signs
  - atrophy, pigment changes,
- inflammatory signs
  - hemorrhages, microaneurysms
  - retinal exsudates, retinal edema
  - Sheathing, narrowing, dilatation







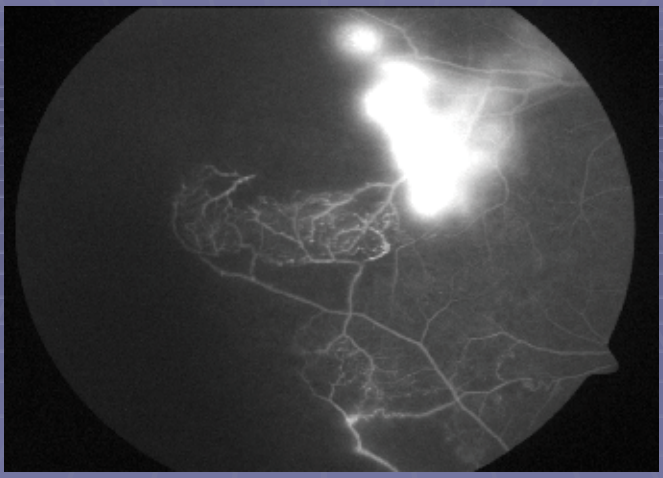


Examples for Vitreous Changes

- Vitreous Haze

Examples for Angiographic Changes

- Staining of vessel walls
- Neovascularization
- Vascular occlusion
- Non Perfusion



Examples for other Pathologic Findings

- Autoantibodies (ANA,ANCA)
- ACE, urinalysis
- various serologies
- TB-testing: Mantoux or Quantiferon
- Biopsy or diagnostic ppV

Planned Study for identifying retinal vasculitis terms?

- **Analyse patients for 1-2 years**
- **picture fits to "vasculitis"**
- **retrospective, prospective**
- **identify the development**
  - **terms**
  - **extension**
  - **associated disorders**

Timetable

- Glossary: Wakefield, other organizers
- Data bank: Ness (has to be adapted)
- Official Invitation for participation: app. 5-2011
  - Retrospective analysis of 100-200 cases of retinal vasculitis for 2 years
  - 20-30 centres
  - appr. ½ year
- finishing evaluation: app. 2013
- next step: severity score

Book
Intraocular Inflammation

- Editors
- M. Zierhut, F. Orefice, S. Ohno, C. Pavesio, N. Rao
- Springer NYC
- CD/DVD with appr. 100 case reports

Interested ?

- Case Reports
- Dynamic in disease during the follow up
- Unusual cases
- Manfred.zierhut@med.uni-tuebingen.de

Manfred Zierhut, Centre of Ophthalmology , Tuebingen, Germany

Notes

Behçet's disease

Ilknur Tugal-Tutkun, Turkey

15

ABSTRACT

Behçet's disease is a multisystem inflammatory disorder that is most common in countries along the ancient "Silk Road". The eye is the most commonly involved vital organ in Behçet's patients and the typical form of involvement is a relapsing remitting panuveitis and retinal vasculitis. Uveitis is the initial manifestation of the disease in 10-15% of the patients. Anterior uveitis is always nongranulomatous. Diffuse vitritis, retinal infiltrates, sheathing of predominantly retinal veins, and occlusive vasculitis are the typical signs of posterior segment inflammation. Spontaneous resolution of acute inflammatory signs is a diagnostic feature. Fundus fluorescein angiography is the gold standard in monitoring inflammatory activity. Laser flare photometry is a useful noninvasive tool since flare readings correlate with fluorescein angiographic leakage. The most common complications are cataract, maculopathy, and optic atrophy. Male patients have a more severe disease course and worse visual prognosis. Immunomodulatory therapy is indicated in all patients with posterior segment involvement. Corticosteroids combined with azathioprine and/or cyclosporine is used initially. Biologic agents, including interferon alfa and infliximab, are used in resistant cases. Visual prognosis has improved in recent years with an earlier and more aggressive use of immunomodulatory therapy and the use of biologic agents in resistant cases.

Key words: Behçet's Disease, Immunomodulatory Treatment, Retinal Vasculitis, Uveitis

DOI: 10.4103/0974-9233.58425

INTRODUCTION

Behçet's disease is a multisystem inflammatory disorder of unknown etiology. It was named after the Turkish dermatologist, Professor Hulusi Behçet, who described the triple-symptom complex of the disease, recurrent oral ulcers, genital ulcers, and iritis, as a distinct entity in 1937.[1] The disease is now recognized as a systemic vasculitis involving many organ systems and leading to a wide spectrum of manifestations.[2]

EPIDEMIOLOGY

Although Behçet's disease occurs worldwide, it has the highest prevalence in countries between the northern latitudes of 30 and 45 degrees along the ancient "Silk Road" from the Mediterranean basin to the far East.[3,4] The highest prevalence rates have been reported from Turkey (up to 420 per 100,000).[5] The disease is strongly associated with the major histocompatibility complex antigen HLA-B51.[6] The global distribution of this antigen among healthy control populations roughly corresponds to the overall distribution of the disease.[3]

ETIOPATHOGENESIS

The etiopathogenesis of Behçet's disease has not been clarified. It is generally accepted that in immunogenetically susceptible individuals, environmental agents may trigger an enhanced and dysregulated immune response resulting in inflammatory vascular injury in many organ systems.[7] A dysregulation of both innate and adaptive immune systems is implicated in the pathogenesis.[7,8]

DEMOGRAPHICS

Behçet's disease primarily affects young adults. The age of onset of the disease is typically in the third or fourth decade of life. Onset of disease in childhood or at an advanced age is rare.[9-11] Most pediatric cases are diagnosed in late childhood.[9,10] Although both genders are equally affected in large series, male patients have a more severe course with more frequent involvement of vital organs.

Department of Ophthalmology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey

Corresponding Author: Prof. Ilknur Tugal-Tutkun Istanbul Tip Fakultesi Goz Hastaliklari A.D., Capa 34390, Istanbul-Turkey.
E-mail: itutkun@istanbul.edu.tr

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DIAGNOSIS

The diagnosis of Behçet's disease is based on a combination of clinical findings. There is no specific diagnostic test. Several sets of diagnostic criteria have been developed. The set of criteria proposed by the International Study Group for Behçet's Disease in 1990 was intended for classification of patients; to ensure uniformity of patients recruited for studies.[12,13] Recurrent oral ulcers plus at least two of the following criteria are required for classification: Recurrent genital ulcers, skin lesions, eye lesions, or a positive pathergy test.

SYSTEMIC MANIFESTATIONS

Patients with Behçet's disease have recurrent inflammatory attacks in all organ systems involved.[2,14,15] Mucocutaneous manifestations are the hallmark of the disease. Recurrent painful oral ulcer, indistinguishable from common aphthae, is the earliest sign of the disease in majority of the patients. However, most patients do not seek medical attention until the development of other manifestations. Genital ulcers are painful and heal with scarring. A variety of skin lesions may be seen during the course of the disease, including erythema nodosum, superficial thrombophlebitis, papullopustular lesions, pseudofolliculitis, acneiform lesions, and rarely extragenital ulcerations. A hyperreactivity to nonspecific trauma is a pathognomonic feature of Behçet's disease. The skin pathergy reaction is defined by the development of papulopustular lesions at skin prick sites at 48 hours. Similar hyperreactivity can also be induced following trauma at other sites such as the joints, oral and genital mucosa, and conjunctiva. Arthralgias are common, but true arthritis develops in around 30% of the patients. The arthritis attacks are usually non-erosive, most commonly involving the knees and ankles. A chronic destructive arthritis is very rare. Gastrointestinal ulcers, neurological involvement, and major vessel disease are uncommon life-threatening complications of the disease.[16] Gastrointestinal involvement is more common in the Japanese population than in the Mediterranean and the Middle Eastern populations. Ileocaecal region of the gastrointestinal tract is most frequently affected and may cause perforation. There are basically two types of neurological involvement: Parenchymal involvement which is mainly a meningoencephalitis most frequently affecting the brainstem structures and non-parenchymal involvement or vascular neuro-Behçet which represents mainly dural sinus thrombosis.[17] Parenchymal neurological involvement has a worse prognosis with a higher rate of morbidity and mortality. Dural sinus thrombosis is more frequently seen in patients with vascular Behçet which is defined by deep venous thrombosis and arterial aneurysms and less commonly arterial occlusions.

OCULAR INVOLVEMENT

The eye is the most commonly involved vital organ in Behçet's disease. Uveitis is reported in around 50% of the patients in multidisciplinary settings, but in more than 90% in ophthalmology departments.[14,18] Uncommon or rare types of ocular involvement include episcleritis, scleritis, conjunctival ulcers, keratitis, orbital inflammation, isolated optic neuritis, and extraocular muscle palsies.[2,19-22]

BEHÇET'S UVEITIS

It is classically defined as a bilateral nongranulomatous panuveitis and retinal vasculitis. However, a minority of patients, especially females, may have isolated anterior uveitis. The disease may also remain unilateral for many years in some patients.[23]

The current diagnostic or classification criteria sets do not allow diagnosis of Behçet's uveitis based on ocular findings alone. Uveitis is the initial manifestation in around 10-15% of the patients with ocular involvement. Therefore, it is important to recognize Behçet's uveitis as a distinct entity that can be diagnosed in the absence of systemic manifestations. There are some pathognomonic findings that suggest the diagnosis at a single ocular examination in some patients. In most other cases, however, one needs to follow the patient and observe the characteristic clinical course.

Similar to the recurrent nature of the other manifestations of the disease, Behçet's uveitis runs a relapsing and remitting course. Sudden onset of uveitis attacks and spontaneous resolution of acute inflammatory signs are the rule and should be used as a diagnostic feature. Vision may be severely affected at the onset of explosive uveitis attacks but usually improves remarkably following the resolution of intraocular inflammation.

At a given episode of activation, acute inflammatory signs may be seen in the anterior or posterior segments of the eye or more commonly in both. Ciliary injection is not a constant feature in eyes with anterior segment inflammation. It may be disproportionately mild in eyes with severe anterior uveitis. A "cold" hypopyon resembling the pseudohypopyon, seen in masquerade syndromes, is not uncommon. Endothelial dusting is seen in eyes with a high grade of anterior chamber cells. Granulomatous keratic precipitates are not compatible with the diagnosis of Behçet's uveitis. A hypopyon is reported in 10-30% of the patients [Figure 1a]. Its incidence may be higher than the reported Figures because it may be missed if the patient is not seen at the onset of the uveitis attack. The hypopyon forms and dissolves rapidly. It typically forms a smooth layer and shifts freely with head positioning. In eyes with a hypopyon, there is almost always severe inflammation in the posterior

segment. These features help differentiate Behçet hypopyon from HLA-B27 hypopyon, which is always "hot" and sticky, and with inflammation confined to the anterior segment.

Diffuse vitritis is a constant feature of posterior segment involvement. Vitreous haze is an indicator of inflammatory activity and is most severe at the onset of uveitis attacks. In severe attacks, the fundus reflex may be lost. If the fundus can be visualized, one may see hyperemia and swelling of the optic disc, diffuse inflammatory sheathing of the retinal veins, retinal infiltrates, branch retinal vein occlusions, and/or exudative retinal detachment. These acute inflammatory signs do not get worse, but gradually resolve even without treatment. Spontaneous resolution is an important diagnostic feature. However, new attacks may occur with new infiltrates or occlusive vasculitis of different branches, before the complete resolution of previous signs. Transient superficial retinal infiltrates that denote activation are considered as one of the pathognomonic findings [Figure 1b]. They may be in any number or location and resolve within a few days, usually without leaving any visible scarring. Deeper retinal infiltrates that may be sometimes difficult to distinguish from infectious retinal infiltrates may take longer to resolve and may leave scars. Another pathognomonic finding is the accumulation of inflammatory precipitates on the surface of the inferior peripheral retina during the resolution of diffuse vitritis [Figure 1c]. They appear several days after the onset of an attack and resolve within a few weeks without leaving any sequelae.

Periphlebitis, a hallmark of Behçet's vasculitis may be both leaky and occlusive. Although retinal arterioles and capillaries are also involved, arteriolitis is not seen without periphlebitis and capillaritis can be best demonstrated by fluorescein angiography. Sheathing of retinal veins might be difficult to visualize at the onset of an acute episode but may become readily visible when diffuse gliotic sheathing appears after the resolution of acute inflammation. More severe breakdown of the blood-retina barrier may cause a fundus picture resembling frosted-branch angiitis, also with hemorrhages all along the inflamed retinal vascular tree. Occlusion of retinal veins may occur at any location from the central retinal vein to the tiny small branches, and it is recurrent [Figure 2a]. After the resolution of retinal hemorrhages, ghost vessels are seen on ophthalmoscopy, and fluorescein angiography may show extensive retinal capillary nonperfusion. Neovascularization of the disc (NVD) or elsewhere (NVE) may develop as a complication of retinal ischemia. However, NVD is more commonly induced by uncontrolled intraocular inflammation. We have reported retinal ischemia in only 13% of eyes with NVD associated with Behçet's uveitis.[24]

Laser flare photometry and fundus fluorescein angiography are the most useful tools in monitoring Behçet's uveitis.[25-27] In between attacks, that is, in the absence of acute inflammatory signs such as anterior chamber cells, retinal infiltrates, or inflammatory sheathing of retinal veins, it may be difficult to determine clinically whether the eye is completely quiet or not. Persistent vitreous haze, hyperemia of the optic disc and blurring of its margins, and macular edema are signs of inadequately controlled intraocular inflammation. Fluorescein angiography is the gold standard to monitor persistent intraocular inflammation which is demonstrated by persistent retinal vascular leakage. It also shows the presence and extent of retinal ischemia [Figure 2b]. Fluorescein angiography is not helpful in eyes with poor visualization of the fundus due to extensive posterior synechiae, cataract, or significant vitreous haze. Anterior chamber flare readings measured by laser flare photometry correlate not only with inflammatory signs in the anterior segment, but also with inflammatory signs in the posterior segment.[25] Flare readings correlate with fluorescein angiographic leakage in eyes in clinical remission.[25] We use laser flare photometry on a routine basis as an objective, quantitative and noninvasive measure of intraocular inflammation in Behçet's patients. The risk of a recurrent uveitis attack is higher in patients with flare readings higher than 6 photons/msec than in patients with lower flare readings.[25]

The most common complications of Behçet's uveitis are cataract, posterior synechiae, macular edema, optic atrophy, and glaucoma.[18,23] Retinal neovascularization, retinal tears and

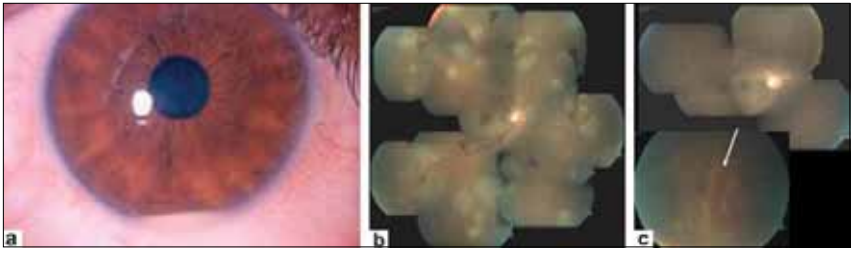

Figure 1: (a) A 27 year-old pregnant woman with Behçet's disease presented with a hypopyon panuveitis; (b) with multifocal retinal infiltrates; (c) Spontaneous resolution of the retinal infiltrates and accumulation of precipitates on the surface of the inferior peripheral retina were noted one week later

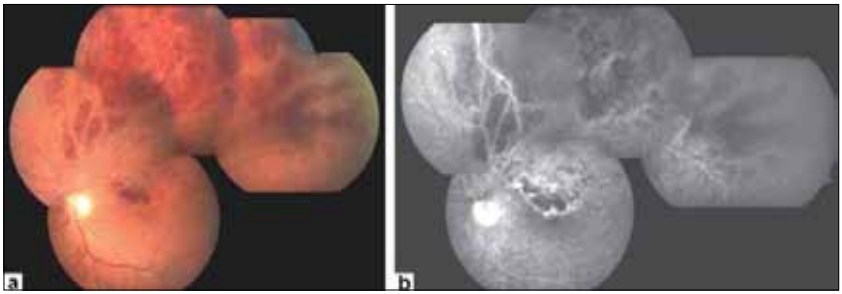

Figure 2: (a) Color fundus photograph of the left eye of a patient with Behçet's disease shows retinal hemorrhages at the posterior pole and at the superior temporal quadrant following an episode of superior temporal branch retinal vein occlusion; (b) fluorescein angiography shows staining of the optic disc as well as inflamed retinal vessels and hypofluorescence due to retinal hemorrhages and nonperfusion of the retinal vasculature at the involved quadrant

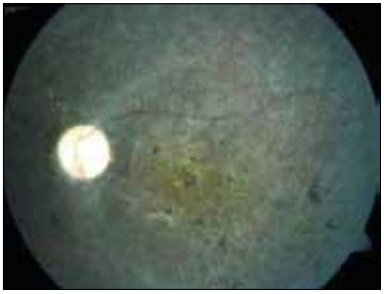

Figure 3: Color photograph shows end-stage fundus picture in the left eye of a patient with Behçet's disease. Please note optic atrophy, gliotic vascular sheathing, ghost vessels, and diffuse retinal atrophy with pigmentation resembling retinitis pigmentosa

detachment, macular hole, and hypotony or phthisis bulbi are uncommon or rare complications. The most common causes of permanent visual loss are maculopathy and optic atrophy. The end-stage fundus picture is characterized by optic atrophy, ghost vessels, diffuse atrophy and gliosis of the retina with variable pigmentation and macular scarring[23] [Figure 3]. The vitreous is remarkably clear at the end stage.

VISUAL PROGNOSIS AND TREATMENT

The frequency and severity of uveitis attacks show individual variability. Although some attacks may cause permanent loss of useful vision, recurrent attacks and cumulative damage usually determine the visual outcome. In general, young males have a more severe disease course and worse visual prognosis.[28] Other risk factors that have been postulated as indicators of poor visual prognosis include skin lesions, arthritis, neurologic involvement, vascular thrombosis, posterior uveitis attacks, more than three uveitis attacks per year, strong vitreous opacity, exudates within the retinal vascular arcade, and fluorescein angiographic findings of NVD and macular ischemia.[29-31] Recent reports from Japan suggest that improvement in the environment or health care may lead to a change in the epidemiological features of the disease over time in populations with a stable genetic makeup.[32,33] In a study of Japanese patients, Yoshida *et al*. reported a reduction in the frequency of uveitis attacks and in the need for cyclosporine or cyclophosphamide therapy, and an improvement of visual prognosis in the 1990s compared to the 1980s, suggesting a trend to milder disease in the Japanese population.[32]

In a retrospective cohort study conducted in the United States, the rate of loss of visual acuity to 20/200 or worse was 0.09 per eye-year.[34] In an international retrospective survey, one quarter of the patients had poor vision (< 0.1).[35] Visual outcome was analyzed by the Kaplan-Meier method in two large series reported from Turkey and China.[18,23] The estimated risk of loss of useful vision at 10 years was 30% in males and 17% in females in the Turkish study.[23] By comparison, these Figures were 65% and 33%, respectively, in the Chinese study.[18] The authors explained this difference by late referral and noncompliance of Chinese patients with treatment and follow-up visits because of long traveling distances or economic reasons. They stated that visual outcome was better in patients who received early treatment and were compliant with treatment. In the Turkish study, visual outcome was better in patients who presented in the 1990s compared to those who presented in the 1980s.[23] This was explained by an earlier and more aggressive immunosuppressive treatment of patients in the 1990s. Khairallah *et al*., also reported better final visual acuity in Tunisian patients where immunosuppressive drugs were used as first line therapy after 2001.[36] In all of these series, only conventional immunosuppressive agents were used.

Behçet's uveitis is one of the absolute indications of immunomodulatory therapy. However, in patients with strictly anterior uveitis, there is no need for systemic treatment. Cells in the posterior vitreous cavity and any leakage on

fluorescein angiography should be considered as an indication for immunomodulatory therapy even if there is no other clinical sign in the posterior segment. Systemic corticosteroids should be used only in patients with active inflammation with an immediate threat to vision. A slow tapering of corticosteroids is important because rebound attacks may be more severe than the natural course of the disease. The use of colchicine as an anti-inflammatory agent is limited to mucocutaneous and joint manifestations because it does not have any effect on eye disease. Among the conventional immunomodulatory agents, both azathioprine and cyclosporine have been shown to be effective in controlled trials.[37,38] A combination of these agents may be used when monotherapy fails.[39] Cyclosporine may be combined with mycophenolate in patients who do not tolerate azathioprine. Cyclosporine is contraindicated in patients with neurological involvement.

The use of alkyllating agents is limited due to their potential serious side effects. Further, cyclosporine has been shown to be superior to intravenous pulsed cyclophosphamide in a comparative study,[40] and there is no controlled study with chlorambucil. According to the recently published evidence based EULAR recommendations, any Behçet's patient with posterior segment involvement should be treated with azathioprine and corticosteroids, and any patient with severe eye disease should receive either cyclosporine or infliximab infusions combined with corticosteroids and azathioprine; or alternatively interferon alpha therapy.[41]

The introduction of biologic agents into the therapeutic armamentarium has enabled prevention of visual loss in most severe cases of Behçet's uveitis. Although there are no controlled trials yet, remarkable results have been reported with the use of interferon alfa and anti-TNF alfa monoclonal antibody, infliximab, in patients with Behçet's uveitis resistant to conventional treatment.[42-51] Interferon alfa is effective in over 90% of such cases.[42-45] The main advantage of this agent over other therapeutic regimens seems to be the induction of long-term remissions after discontinuation of treatment.

A single infusion of infliximab 5 mg/kg suppresses the intraocular inflammation rapidly in Behçet's patients. Therefore, it can be used for the treatment of severe attacks with a high risk of structural damage and permanent visual loss.[46,47] However, repeated infusions need to be administered for the prevention of recurrent attacks. Behçet's patients with severe uveitis usually require infusions at intervals shorter than 8 weeks.[48] Lack of a sustained remission, high cost of treatment, and major safety issues limit the long-term use of infliximab. Furthermore, resistance may develop after prolonged treatment because of the development of antibodies against the murine component of infliximab. A limited number of patients who successfully switched from infliximab to adalimumab, a humanized monoclonal anti-TNF antibody, have been reported in the literature.[52,53]

Different health care systems, economic status of different countries, and high cost of biologic agents may limit the physicians' therapeutic choices. For example, infliximab has been approved for the treatment of Behçet's uveitis only in Japan, but still remains as an off-label treatment in other countries. Our stepwise therapeutic approach in Turkish patients is determined by our healthcare system. We use azathioprine and/or cyclosporine as the initial choice of treatment in patients with posterior segment involvement. Corticosteroids are combined on an individual basis. When the disease is not controlled with the triple-agent regimen that includes azathioprine, cyclosporine, and low-dose steroids or when this regimen is not tolerated, we administer interferon alfa monotherapy. We use infliximab only in patients who fail or do not tolerate interferon alfa therapy. With this approach visual prognosis of our patients has improved in the 2000s compared to the 1990s.

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Intermediate uveitis

EUPO COURSE
SOE
GENEVA 2011

Miles Stanford
Medical Eye Unit
St Thomas' Hospital
London

Intermediate Uveitis – Definition

- Intraocular inflammation that mainly affects the peripheral retina, pars plana and ciliary body
- Pars planitis is a variant

L'INFLAMMATION DE LA RÉGION
DE L'« ORA SERRATA » ET SES SÉQUELLES (1)

par M. Charles L. Schepens

La région avoisinant l'ora serrata, étudiée dans ce travail, s'étend de 2 à 4 millimètres de chaque côté de la ligne de l'ora.

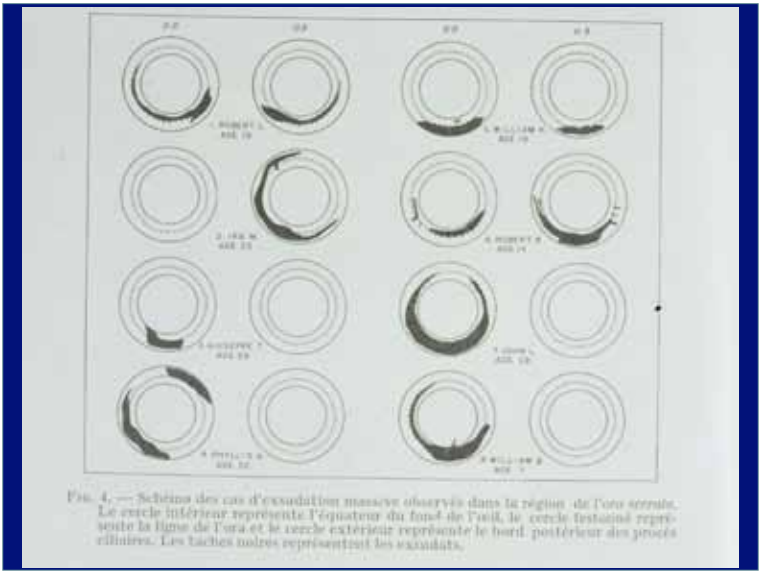


FIG. 4. — Schéma des cas d'exsudation massive observés dans la région de l'ora serrata. Le cercle intérieur représente l'équateur du fond de l'œil, le cercle festonné représente la ligne de l'ora et le cercle extérieur représente le bord postérieur des procès ciliaires. Les taches noires représentent les exsudats.

Intermediate Uveitis – Epidemiology

- Prevalence 1:15,000 general population
- Incidence 1.4/100,000/year
- Age of onset appears to have two peaks
  - 5-15 years
  - 15-35 years
- Disease onset is rare after age 40
- Males slightly more commonly affected
- Rare in the Far East

Intermediate Uveitis – Pathology

- Uvea is rarely involved
- Lymphocytic cuffing of peripheral retinal vessels
- Snowbank – Collapsed vitreous
  - Astrocytic proliferation
  - Neovascularisation
  - Lymphocytes
- Snowball – Vitreous granuloma (epithelioid and giant cells)

Intermediate Uveitis - Aetiology

- Unknown
- Possibly autoimmune (nb MHC class 2 associations)
- Altered vitreous is a possible antigen
- Similar clinical picture reported in primate eyes following repeated injection of hyaluronic acid

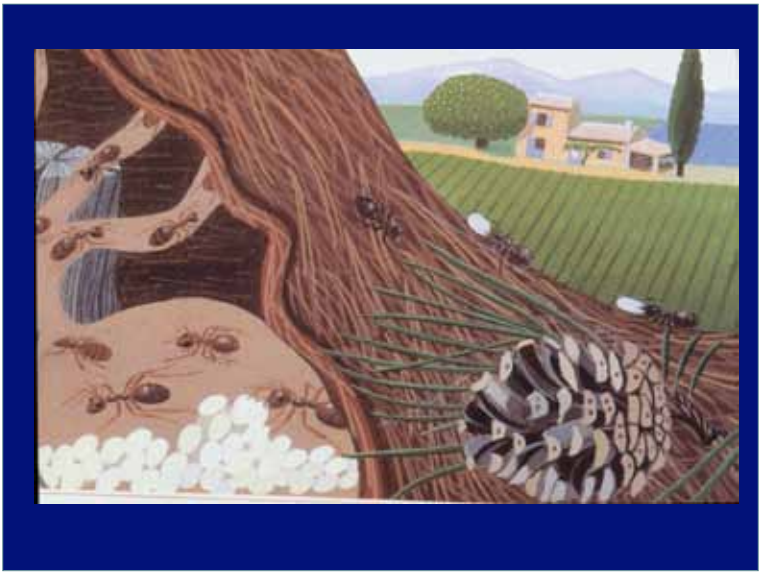
Intermediate Uveitis - Symptoms

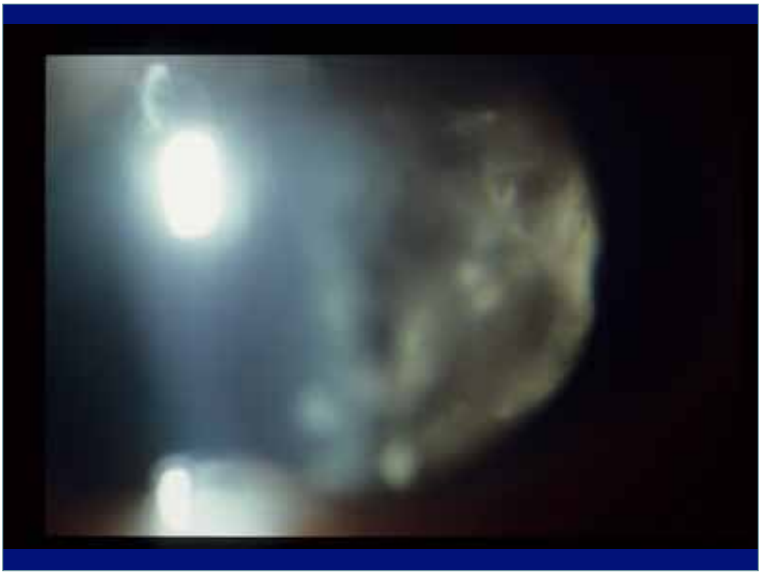
- May be asymptomatic
- Blurring/floaters
- Anterior uveitis is mild
- 75% have bilateral disease on presentation

Intermediate Uveitis - Signs

- White eye with mild, non-granulomatous uveitis
- Vitreous infiltration (snowballs)
- Pars plana exudate (snowbanking)
- Snowbank is usually inferior but may be 360^0
- Retinoschisis
- Neovascularisation (vitreous haemorrhage)
- Retinal vasculitis
- Cystoid macular oedema

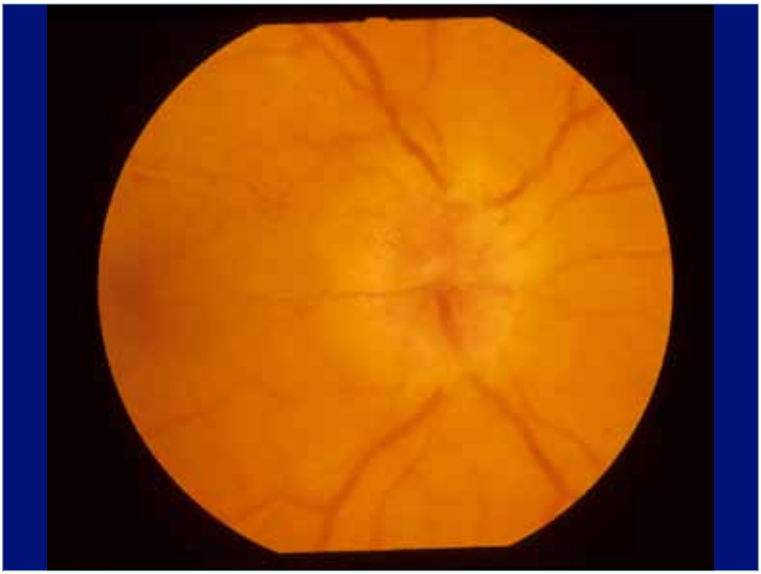
‘Oeufs des formis’

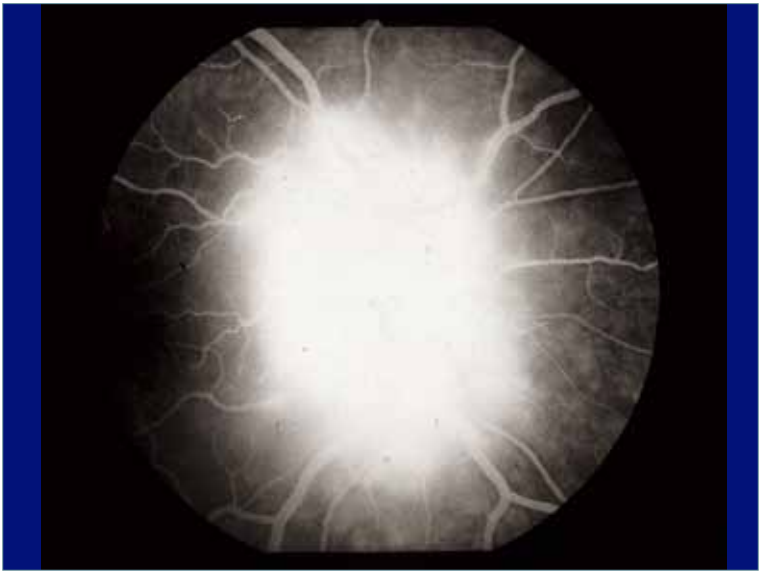


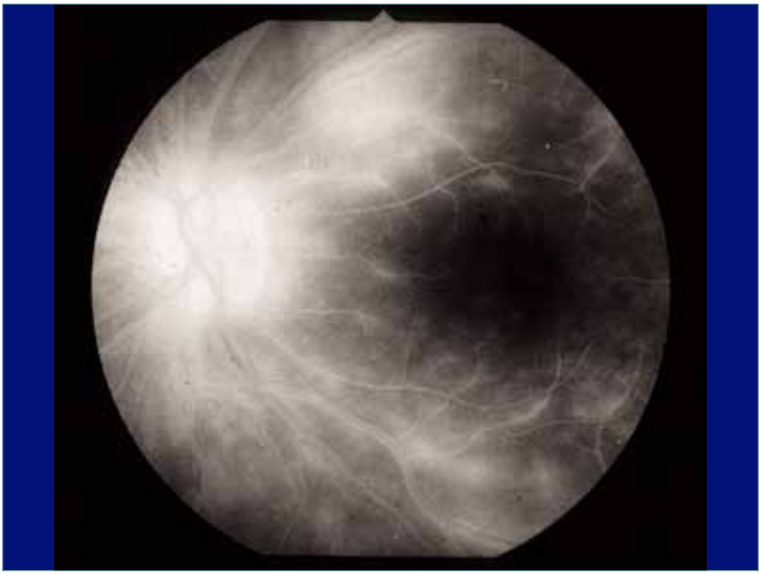


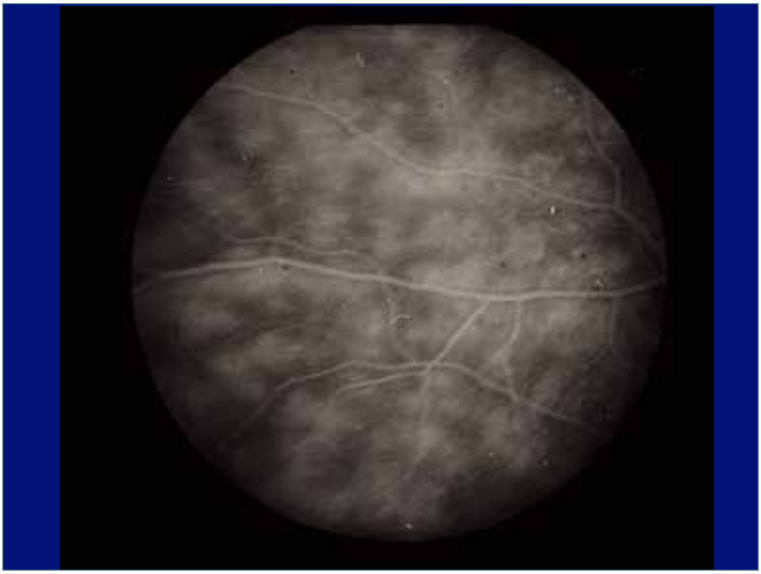
Intermediate Uveitis- Investigation of visual loss

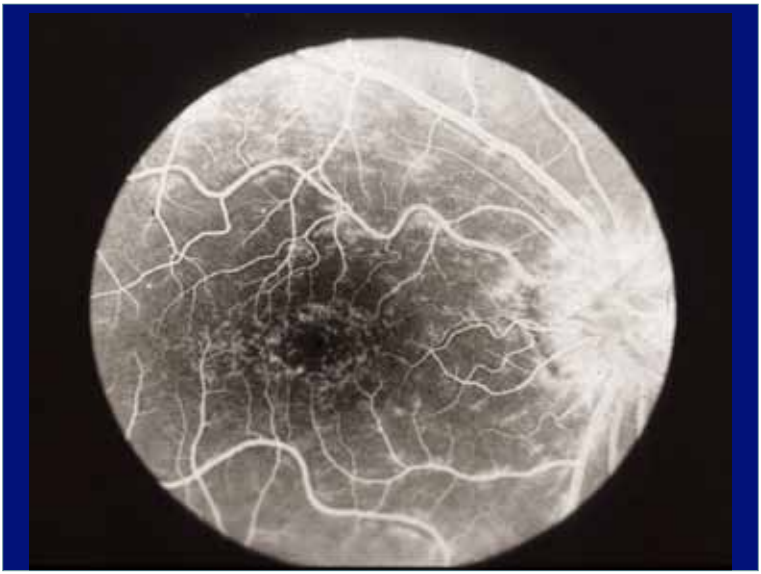
- Fluorescein angiography
- Optical coherence tomography

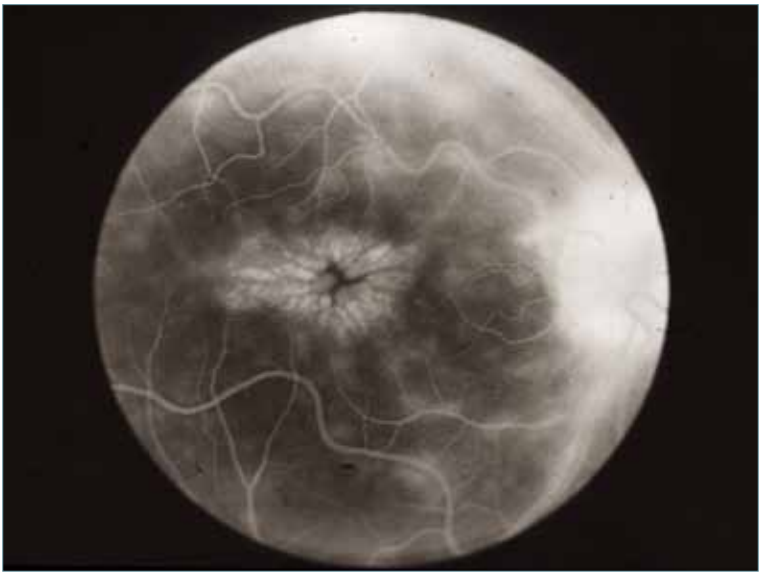


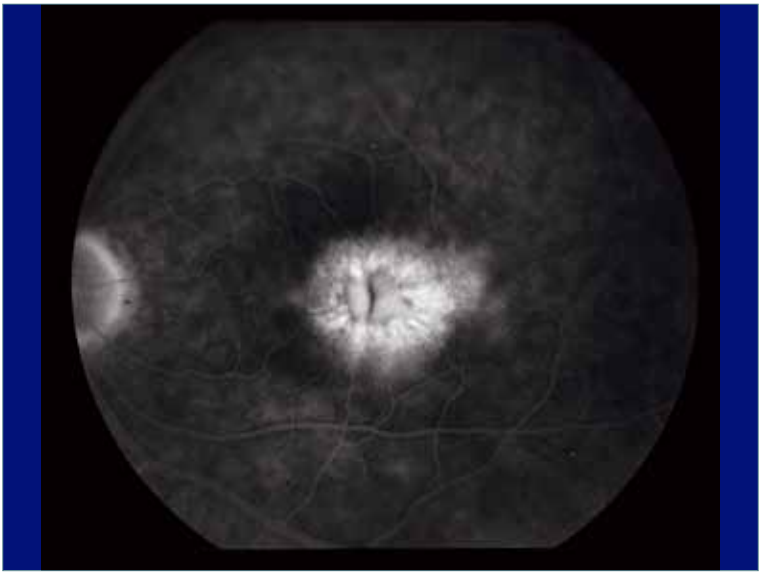








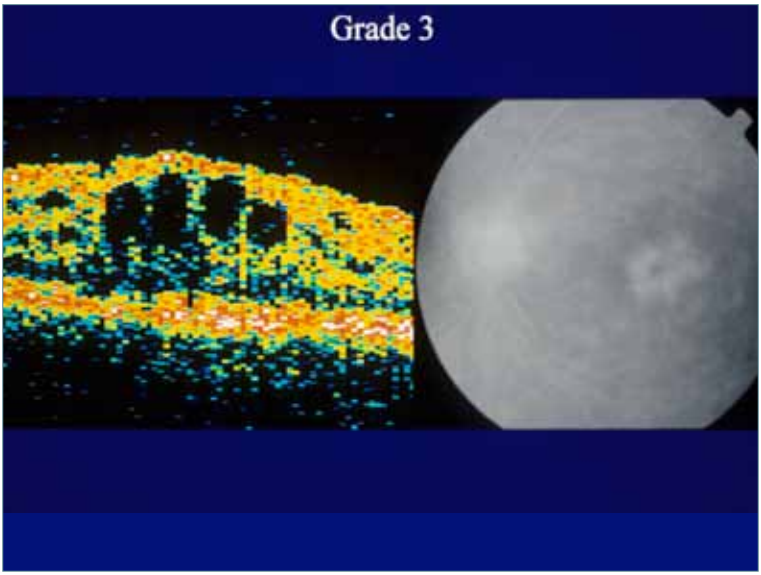




Intermediate Uveitis – Angiographic findings

- Leakage from peripheral retinal veins
- Cystoid macular oedema
- Leakage from the optic disc
  - common in children
- Evidence of neovascularisation

Optical Coherence Tomography

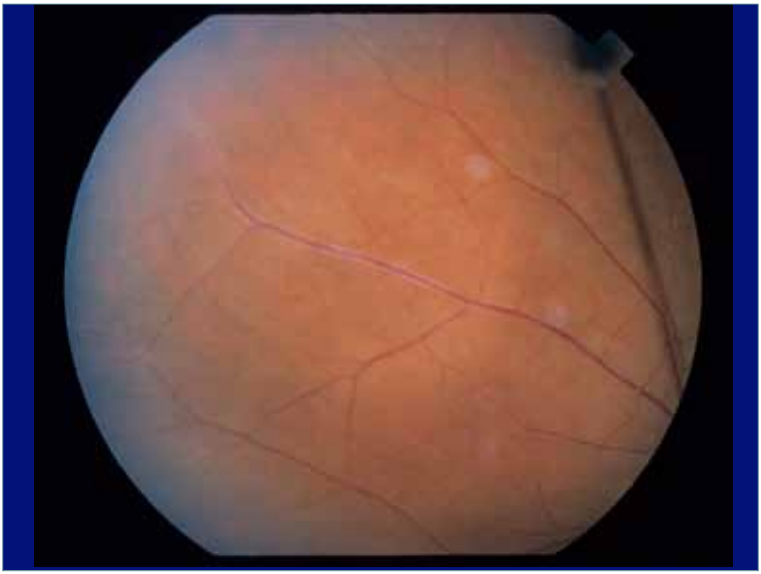


Intermediate Uveitis – Differential diagnosis

- Ocular infection – syphilis, Lyme, HIV (especially immune recovery), HTLV-1, TB, early endogenous endophthalmitis
- Ocular malignancy esp. lymphoma
- Systemic granulomatous disease, MS, sarcoid
- Rarely – Fuchs', Eales', VKH, ocular ischaemia

Intermediate Uveitis – Systemic Associations

- Multiple Sclerosis
- Sarcoidosis



Intermediate Uveitis and Multiple Sclerosis

- 20% hospital patients with MS have asymptomatic uveitis
- 2% have symptomatic uveitis
- 20-30% of patients presenting with intermediate uveitis develop MS within 5-7 years
- Similar HLA association - DR*1501

HLA typing in Pars Planitis

Malinowski et al Ophthalmology 1993, 100;1199

40 patients v. 350 controls

	Patients	Controls	RR
HLA B8	37%	20%	2.44
HLA B51	22%	12%	2.16
HLA DR2	67%	28%	5.32

HLA DR15 and Intermediate Uveitis

Tang et al AJO 1997. 123;70-5

- 72% of patients – DR15 positive (versus 28% controls: RR = 6.3)
- DRB1*1501 in all
- Association with other DR 15 related diseases
  - Multiple Sclerosis
  - Idiopathic optic neuritis

Intermediate Uveitis – Complications

- Cataract - <60%
- Glaucoma - <10%
- Cystoid macular oedema - <50%
- Pre-retinal membranes – <35%
- Retinoschisis
- Vitreous haemorrhage - <6.5%
- Retinal detachment – 6-12%

Intermediate Uveitis – Treatment

- Only treat if VA <6/12 (unless NVs)
- Try periocular steroids
- Systemic immunosuppression if bilateral or resistant to periocular steroids

Treatment of Posterior Uveitis
Orbital steroid injections

Study	Patients (eyes)	Increased VA	Improved Inflammation
Tanner et al	28 (28)	12/28(43%)	21/28 (75%)
Jennings et al	10 (12)	6/12(50%0	N/A
Riordan-Eva et al	28 (54)	19/47(40%)	13/51 (25%)
Helm et al	20 (20)	12/18(67%)	N/A
Dafflon et al	53 (58)	67%	N/A

Intermediate Uveitis – Surgical treatment

- Cryotherapy to the pars plana
- Vitrectomy
- Cataract extraction, etc
- Surgery when diseased eye is as quiet as possible

Visual Outcome in Intermediate Uveitis

Study	No Patients	Years	% final VA >6/12
Smith	100	10	75%
Malinowski	54	7	90%
Raja	54	2	90%
Dean	48	2	85%
STH	53	5	60%

Intermediate Uveitis Prognosis

Visual outcome

Benign course in 30%
Stable course in 40%
Relapsing sight threatening course in 30%
Visual Prognosis is good

Systemic outcome

Multiple sclerosis

Premature vascular disease

Aphorisms in Intermediate Uveitis

Visual acuity will be the same at the end of the disease as at the beginning

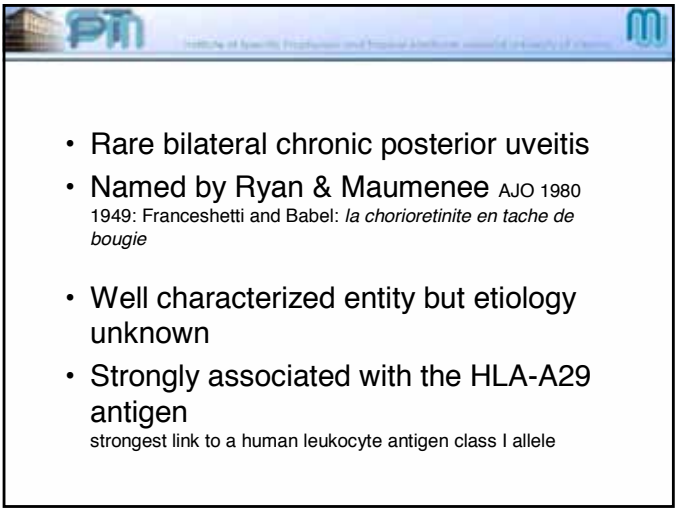
People who do well start well

The disease usually outlives the practising lifetime of the ophthalmologist looking after it

Miles Stanford
Medical Eye Unit
St Thomas' Hospital
London

Notes


CENTER FOR GEOGRAPHIC MEDICINE
Birdshot Chorioretinopathy
Talin Barisani-Asenbauer
LB- Centre for ocular inflammation & infection


• Rare bilateral chronic posterior uveitis
• Named by Ryan & Maumenee AJO 1980
1949: Franceshetti and Babel: *la chorioretinite en tache de bougie*
• Well characterized entity but etiology unknown
• Strongly associated with the HLA-A29 antigen
strongest link to a human leukocyte antigen class I allele

- <1.5% of all uveitis cases,
  <8% of patients with posterior uveitis
- middle age patients (white)
- gender: some report f>m, some f=m
- no association with systemic disease
  Kiss S et al Int. Ophthal. Clinics 2006
- extraocular manifestations reported:
  hearing loss, hypertension, allergies, psoriasis
  Pagnoux et al. Presse Med 2010;39:e97-e102.
- ~10% of patients are legally blind

symptoms

- Blurred vision
- Floaters
- Night blindness
- Poor contrast sensitivity
- Distorted vision
- Photopsias

diagnosis

- Clinical appearance
- ICG
- HLA-A29 typing
- Anxillary tests: CP, autofluorescence, FLA, dark adaptation, microperimetry, EOG/ERG

clinical appearance

- Quiet, not painful eye
- Minimal anterior segment inflammation
- No posterior synechiae
- Chronic vitreous cells, low grade vitreous haze
- Retinal vascular leakage (perifoveal capillaries)
- No snowballs or snowbank
- Cardinal marker: multiple, distinctive, hypopigmented, cream colored lesions scattered troughout the fundus
  cave: spectrum of presentations!

Birdshot lesions

- Typically oval or round in shape, uniform in color (cream colored)
- Symmetrical and regular distribution
- Can be subtle
- Level of choroid
- Size: ~1/4 optic disc Ø
- Location: clustered around the optical disk
  petaloid appearance and along the vascular arcade
  lesions radiate from optic disc to periphery
  in the periphery lesions can become confluent
- **Absence of pigmentation of the lesions**
- Histology: Gaudio et al described aggregation of the lymphocytes with their foci in the deep choroid, in the optic nerve head and along the retinal vasculature with a vasotropic distribution. (BJO 2002)

Fluorescein angiography

- When the RPE and choriocapillaris are intact lesions: isofluorescent and undectable
- After disruption: hypofluorescence in the early phase and hyperfluorescence in the late phase.
- Retinal vascular system and cystoid macular edema
  - Delayed in the filling time and prolongation of the arteriovenous transient phase
  - Hyperfluorescence of the optic disc and the macula (cystoid macular edema)

Indocyanine green angiography (ICG)

- well-delineated hypofluorescence choroidal spots in the mid phase
- Vasotropic distribution by medium- to large-sized choroidal blood vessels.
- ICG reveals more lesions

OCT

- Cystoid macular edema
- Epiretinal membrane
- Photoreceptor atrophy
- RPE degeneration underneath the areas of photoreceptor involvement
- Anatomical disorganization
- Ultra-high resolution OCT imaging may help in understanding and monitoring the progression

Electrophysiologic testing

- May ellucidate changes in color perception or night vision.
- Electro-oculograms (EOG) and electroretinograms (ERG) are affected.
- abnormal electrophysiologic test may help in the differential diagnosis

HLA-A29

- 80-93.1% HLA-A29 positivity vs 7% in general population
- relative risk ratio from 50 to 224.
- strongest HLA association with any known disease.
- LeHoang et al (AJO 1992): HLA-A29 type 2 subtype
- several cases with A*2901 reported (Levinson RD, AJO 2004; De Waal LP, Immunogenetics 1992)
- 2 patients with A*2910 reported (Donvito B, IOVS 2010)

Differential diagnosis

- Sarcoidosis
- Intraocular lymphoma
- APMPPE
- MCP, PIC
- MEWDS
- Pars planitis
- Posterior scleritis
- Sympathetic ophthalmia
- VKH
- Syphilis
- TbC

Complications

- Chronic cystoid macular edema – 50%
- Epiretinal membrane - 10%
- Macular pucker
- Choroidal neovascularization
- Peripapillary subretinal neovascularization - 6%
- Retinal neovascularization located on the optic disc
- Peripheral retinal neovascularization with capillary nonperfusion
- Optic nerve atrophy
- Others: cataract, glaucoma, rhegmatogenous retinal detachment

Management

- Ocular and systemic steroids to control initial disease
- Longterm treatment with corticosteroid sparing systemic immunomodulatory therapy :

MMF (1-3g/d), IvIg (1.6g/kg every 4 weeks), MTX (7.5-25mg/week), daclizumab(1mg/kg every 2 weeks), adalimumab?, retinoids?

Longterm prognosis

- Prognosis variable: some cases show spontaneous regression but more than 50% worsen
- Longterm visual prognosis without IMT is poor.
- Rothova et al (Ophthalmology 2004):
  55 patients follow up 10 yrs
  5 yrs 30% of eyes legally blind
  10 yrs 40% of eyes legally blind

Management empirical. Need for controlled trials

Talin Barisani-Asenbauer, LB- Centre for ocular inflammation & infection


Use of steroids:
local and systemic
Philip I. Murray
University of Birmingham
Birmingham and Midland Eye Centre
UK
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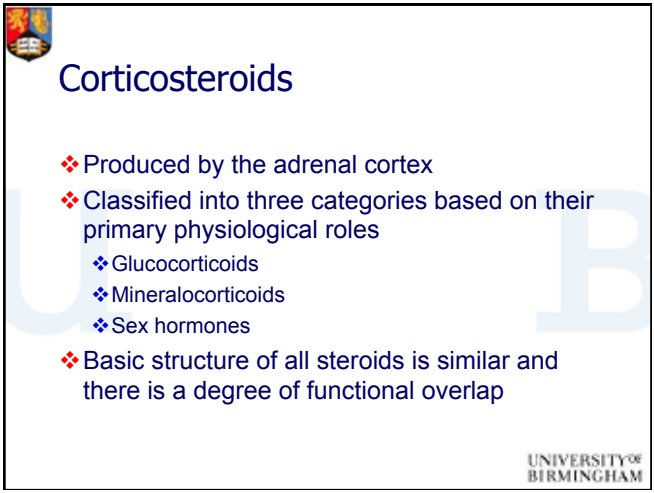
Corticosteroids
Produced by the adrenal cortex
Classified into three categories based on their primary physiological roles
Glucocorticoids
Mineralocorticoids
Sex hormones
Basic structure of all steroids is similar and there is a degree of functional overlap
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Indications

- Topical
  - Anterior uveitis
- Periocular, Intraocular
  - Unilateral non-infectious posterior segment uveitis
- Oral/Intravenous
  - Failure of periocular, intraocular
  - Bilateral non-infectious posterior segment disease
  - Prophylaxis prior to cataract surgery

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Topical corticosteroid preparations in UK

- Betamethasone sodium phosphate 0.1%
- Dexamethasone sodium phosphate 0.1%
- Fluorometholone 0.1%
- Hydrocortisone acetate 1%
- Loteprednol etabonate 0.5%
- Prednisolone sodium phosphate 0.5%
- Prednisolone acetate 1%
- Rimexolone 1%

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Evidence base for topical corticosteroid in AAU

- Disease severity
  - Compared with placebo, corticosteroid eye drops may be no more effective in reducing symptoms of anterior uveitis at 14–21 days compared with placebo
  - Prednisolone 1.0% may be no more effective in reducing anterior chamber cell count compared with rimexolone 1.0%
  - It is not known know whether prednisolone 1.0% may be more effective in reducing anterior chamber cell count at 28 days compared with loteprednol 0.5 %

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- Cure rates
  - Corticosteroid (prednisolone 0.5%, betamethasone 0.1%, dexamethasone 0.1%) may be no more effective in increasing cure rates compared with topical NSAIDs
- Adverse events
  - Prednisolone 1.0% is more likely to increase IOP compared with rimexolone 1.0% or loteprednol 0.5% (high quality evidence)

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GRADE evaluation of topical corticosteroid for AAU

Number of studies (participants)	Year	Outcome	Type of evidence	Comparison	GRADE
1 (60)	1979	Disease severity	RCT	Corticosteroid *vs* placebo	Very low
3 (344)	1996 2004	Disease severity	RCT	Prednisolone 1.0% *vs* rimexolone 1.0%	Low
2 (245)	1999	Disease severity	RCT	Prednisolone 1.0% *vs* loteprednol 0.5%	Low
3 (184)	1982 1985 1991	Cure rates	RCT	NSAIDs *vs* corticosteroid	Very low

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Outcome

- Although corticosteroid eye drops have been the standard treatment for uveitis since the early 1950s, the evidence supporting their effectiveness is somewhat sparse

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Equivalent anti-inflammatory doses of corticosteroids

- Prednisolone 5 mg equivalent to:
  - Betamethasone 750 μg
  - Cortisone acetate 25 mg
  - Deflazacort 6 mg
  - Dexamethasone 750 μg
  - Hydrocortisone 20 mg
  - Methylprednisolone 4 mg
  - Prednisone 5 mg
  - Triamcinolone 4 mg

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Glucocorticoid therapy

- High glucocorticoid activity is of no advantage unless it occurs with relatively low mineralocorticoid activity
- Prednisolone has predominantly glucocorticoid activity and most commonly used for for long-term disease suppression
- The suppressive action of a corticosteroid on cortisol secretion is least when given as a single dose in the morning

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Don't forget!

- Varicella status
- CXR
- BP
- Urinalysis
- Baseline DXA scan
- Steroid card

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Initiation of steroid therapy

- High dose oral e.g. prednisolone 60mg (non-enteric coated) daily for 2 weeks then taper (or 1mg/kg/day)
- 3 iv pulses methylprednisolone 500-1000mg daily or on alternate days in 100ml N/Saline over a minimum of 1 hr

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Administration of oral steroid

- Alternate day therapy
  - Requires a normal or moderately responsive pituitary/adrenal axis
  - Prednisolone causes hypothalamic-pituitary suppression for 12-36 hours
  - Allows the hypothalamic/pituitary axis to regain responsiveness on the day the patient is not receiving the drug
  - May require patient education

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Termination of systemic therapy

- Rate and degree of withdrawal depends on
  - Activity of underlying process
  - Rate of recovery of the endogenous hypothalamic/ pituitary/adrenal axis
- A completely suppressed hypothalamic/ pituitary/adrenal axis may take 9-12 months to recover if the patient was on daily therapy for > 6 months

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Termination of systemic therapy

- No tapering is usually necessary if the patient has been on systemic therapy for < 7-10 days
- Patients on long-term steroid can have daily dosages tapered to 10mg prednisolone fairly rapidly as this level is still above physiological endogenous production
- Below 10mg the dosage must be tapered much more slowly

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Side-effects of steroids

- Systemic
  - Too many to mention
  - Mineralocorticoid
  - Glucocorticoid
- Local
  - Raised IOP
  - Cataract

Balance between benefits and risks

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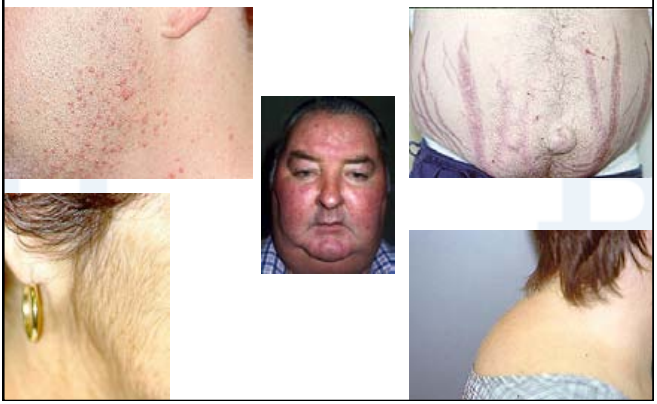
Steroid side-effects



Corticosteroid-induced osteoporosis

- Osteoporosis causes 310,000 fractures in the UK every year at an estimated cost of £1.7 billion each year
- Patients on 5 mg prednisolone or more daily for > 3 months are at risk of osteoporosis
- Fractures can occur within a few weeks of onset of therapy and may be present in up to 30-40% of patients with asthma and rheumatoid arthritis

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- 1 in 3 women and 1 in 12 men > 50 yrs will suffer a fracture of the hip, wrist or spine as a result of osteoporosis
- Bone fractures can cause considerable pain and disability
- 50% of people who suffer a fractured hip lose the ability to live independently
- Around 20% of people who fracture a hip die within a year, as a result of their fracture

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Bone densitometry

- Dual x-ray absorptiometry (DXA scan)
- Lower spine and one hip - two main areas at risk of osteoporotic #
- 1/10th dosage of a CXR and takes 10-20 mins
- Produces a printout of bone density compared to a reference range of young healthy adults
- Difference calculated and expressed in SD: T score
  - 0 and -1 SD (normal)
  - -1 and -2.5 SD (osteopenia)
  - below -2.5 SD (osteoporosis)

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- Among the general population, elevated IOP develops in one third of eyes treated with topical corticosteroids, and topical corticosteroids can further contribute to elevated IOP in eyes of patients with uveitis
- Sustained IOP increases are seen in 22.6% and 34.6% of patients 1 year after a posterior sub-Tenon injection or an intravitreal triamcinolone injection, respectively

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Corticosteroid-induced osteoporosis in patients with uveitis

- 129 uveitis patients
- On steroids for 13 weeks to 31 years (mean 3.6 years)
- Total dosage 1.29 - 166.6g (mean 16.85g)
- Mean daily dose 2.8 - 41mg (mean 13.6mg)
- 62 patients (48%) had additional risk factors for bone loss
- 17 patients (13.2%) used prophylaxis against bone loss

Jones NP et al. Eye 2002;16:587-593

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Corticosteroid-induced osteoporosis

- Bone densitometry:
  - Normal in 72 patients (55.8%)
  - Abnormally low in 57 patients (44.2%)
  - Osteopenia in 37 (28.7%)
  - Osteoporosis in 20 (15.5%)
- Symptomatic fractures in 7 patients
  - 3 had normal bone densitometry
  - 1 had osteopenia
  - 3 had osteoporosis
- Following bone densitometry further action taken in 51 patients

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Steroid-induced cataract

- Posterior subcapsular
- Can be observed 1 year after equivalent dosage of 15mg/day prednisolone
- Occusr in about 25% of patients with RA
- 20mg/day for e.g. 4 years virtually all patients will develop cataract
- Patients with RA have a higher incidence
- Renal transplant patients also more susceptible

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Steroid-induced raised IOP

- NOT a steroid "responder"
- Ocular or systemic administration of glucocorticoids can elevate IOP, depends on:
  - Individual responsiveness
  - Dose and potency of the glucocorticoid
  - Ocular bioavailability and metabolism
  - Route of administration
  - Duration of treatment
  - Genetic disposition

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Counselling of side-effects

- We investigated patient knowledge and understanding of oral corticosteroid side effects, and tried to ascertain the amount of information provided by doctors prescribing these drugs
- Prospective questionnaire survey of 33 patients on oral corticosteroid
- Questionnaire survey of 30 Ophthalmologists of different grades

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Side Effect	Recalled by patients (%)	Told by doctors (%)
Weight gain	69	93
Osteoporosis	34	74
Psychological changes	30	43
Increased blood pressure	24	81
Diabetes Mellitus	21	74
Increased appetite	21	31
Cataract	14	88
Water retention	12	43
Acne	9	31
Peptic ulceration	9	100
Glaucoma	6	74
Myopathy	6	19
Cushing syndrome	6	38
Easy bruising	6	38
Hirsuitism	6	24
Impaired wound healing	3	38
Menstrual changes	3	12
Risk of suddenly stopping treatment	0	74

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Patient information

- Uveitis patient information groups
  - Uveitis Information Group: www.uveitis.net
  - Behçet's Syndrome Society: www.behcets.org.uk
  - Birdshot (chorioretinopathy) Uveitis Society: www.birdshot.org.uk
  - Deutsche Uveitis Arbeitsgemeinschaft e.V.: www.duag.org
  - Inflamoeil: asso.orpha.net/INFLAM
- Generic drug leaflets
  - Arthritis Research UK: www.arthritisresearchuk.org

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Steroid prophylaxis for phakoemulsification

- No standard regime
- A 2 week course of oral prednisolone (0.5mg/kg) tapered postoperatively, produced a better recovery of the BAB than a single dose of intravenous methylprednisolone
- No difference in post-op CMO or visual acuity

Meacock WR et al. Br J Ophthalmol 2004;88:1122-4.

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Do oral steroids always work?

- Percentage of steroid resistant patients
- A subpopulation of steroid refractory (SR) peripheral blood CD4(+) T cells has recently been identified
- Potential target for intervention with anti-IL-2 therapies

Lee RW et al. Invest Ophthalmol Vis Sci 2009;50:4273-8.

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Periocular steroid

- Orbital Floor
- Sub-Tenon
  - Needle (Nozik)
  - Cannula
- Triamcinolone 40mg
- Methylprednisolone 40 mg

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Complications of periocular steroid

- Globe perforation
- Rise is IOP
- Cataract
- Infection
- Fat atrophy

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Complications of intravitreal steroid (triamcinolone 4mg/2mg)

- Endophthalmitis – infective/sterile
- Retinal tear/detachment
- Vitreous haemorrhage
- Rise in IOP
- Cataract

- Duration of action shorter in vitrectomised eyes

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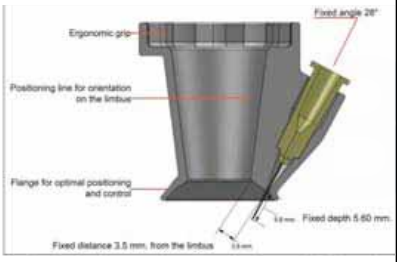
InVitria® - Intravitreal Injection Assistant (Goncalves)



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Fluocinolone acetonide (Retisert implant

- A 3-year, multicentre RCT of the 0.59mg Retisert in 110 patients and the 2.1mg Retisert in 168 patients with non-infectious posterior uveitis
- Uveitis recurrence was reduced in implanted eyes:
  - From 62% to 4%, 10%, and 20% over a 1-, 2-, and 3-year period for the 0.59mg dose group ($p < 0.01$)
  - From 58% to 7%, 17%, and 41% for the 2.1mg dose group ($p < 0.01$)

Callanan DG et al. Arch Ophthalmol 2008;126:1191-201.

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- More implanted eyes than nonimplanted eyes had improved visual acuity ($p < 0.01$
- 0.59mg Retisert implant:
  - 71% of implanted eyes had an IOP increase of 10 mm Hg or more compared with baseline IOP
  - In 51.2%, 22.5%, and 6.1% of eyes, an IOP of 30, 40, and 50 mm Hg or more developed
- Glaucoma surgery was required in 40% of implanted eyes vs 2% of nonimplanted eyes ($p < 0.01$)
- Cataracts were extracted in 93% of phakic implanted eyes vs 20% of phakic nonimplanted eyes ($p < 0.01$)

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Dexamethasone implant (Ozurdex)

- Patients with non-infectious intermediate/ posterior uveitis: 0.7mg and 0.35mg implant groups
- At weeks 8 and 26, both DEX implant groups had significantly lower central macular thickness compared with their corresponding baseline ($p \leq 0.004$) while changes in the central macular thickness of the sham group were not significantly different from the baseline ($p \geq 0.092$)

Lowder C et al. Arch Ophthalmol 2011 Epub ahead of print

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- The proportion of eyes with a vitreous haze score of 0 at week 8 was:
  - 47% with the 0.7mg DEX implant
  - 36% with the 0.35mg DEX implant
  - 12% with the sham ($p < 0.001$)
- This benefit persisted through week 26
- A gain of 15 or more letters from baseline best-corrected visual acuity was seen in significantly more eyes in the DEX implant groups than the sham group at all study visits

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- IOP of 25 mm Hg or more:
  - 7.1% of eyes with for the 0.7mg DEX implant
  - 8.7% for the 0.35mg DEX implant
  - 4.2% for the sham (p > 0.05 at any visit)
- The incidence of cataract reported in the phakic eyes:
  - 9 of 62 (15%) with the 0.7mg DEX implant
  - 6 of 51 (12%) with the 0.35mg DEX implant
  - 4 of 55 (7%) with the sham (p > 0.05)

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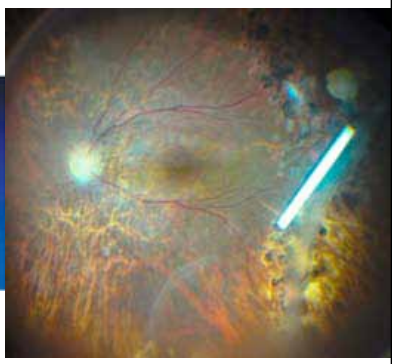

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Key Points

- Corticosteroids are frequently prescribed in ophthalmological practice
- They can be effective first line drugs in uveitis
- BUT they can have very severe side-effects
- You and the patient must be aware of the side-effects
- You need to be able to communicate effectively with patients, doctors and other healthcare workers

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Key points

- In order to be effective treatment must be given
  - For a treatable lesion
  - At an adequate dose
  - Via the most appropriate route
  - For an appropriate length of time
  - Balance risks vs benefit
- Assessment of activity vs damage

Philip I. Murray, University of Birmingham, Birmingham and Midland Eye Centre, UK

Notes

Management strategies for chronic uveitis

Stephan Thurau, Germany

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Immunosuppressive treatment is used as a second line defense in patients with autoimmune uveitis, either chronic or severe anterior, severe intermediate or posterior uveitis. Besides the systemic corticosteroids many other agents can be used as immunosuppressives.

Autoimmune uveitis is mediated by T-helper cells, presumably of the Th1 type, characterized by secretion of interleukin-2 (IL-2), interferon-gamma (IFN-g) and tumor necrosis factor-alpha (TNF-a). These T cells recognize ocular autoantigens and undergo reactivation within the eye, which is followed by secretion of cytokines and chemokines attracting inflammatory cells. These inflammatory cells have the capacity to destroy the delicate structures of the eye and are primarily targeted by antiinflammatory therapies.

Cytotoxic as well as some antibiotic agents and antimetabolites have immunosuppressive effects. Whereas cytotoxic drugs mainly interfere with DNA replication and transcription, some antibiotics and antimetabolites impede the cellular metabolism with respect to cell activation and protein synthesis. The calcineurin inhibitors do interfere with activation pathways for IL-2.

Based on the increasing knowledge of the immune mechanisms that underlie autoimmune diseases, a new group of “biologicals” has been generated. These are immunologically active proteins focussing on specific cells, receptors or ligands, either by blocking inflammatory cytokines (anti-TNF-therapies), by affecting T helper cells (anti-IL2 receptor) or suppressing the autoantigen-specific immune response by induction of mucosal tolerance (oral tolerance).

Intraocular injections of corticosteroids have strong antiinflammatory effects without any systemic side effects, but their use is still limited by the frequency of injections and local, ocular side effects.

Frequently, immunosuppressants are used as steroid sparing agents to control chronic uveitis, requiring systemic steroids at doses that are not acceptable due to their side effects. In those cases a steroid sparing effect may be seen after 1 to 3 months after initiation of immunosuppression. Finally, the dose of steroids should be tapered to an acceptable level, which in general is the Cushing dose, without inducing a flare up. If inflammation soars, then the immunosuppressant must either be replaced by another drug or a second agent must be added to the previous regimen.

Another reason for systemic immunsuppression is a relapsing-remitting uveitis, which causes irreversible damage (i.e. serpiginous choroiditis), in order to prevent any further relapses. In these cases the definition of goals is much more difficult, because the underlying disease activity is unpredictable. This might require continuation of treatment for many years, therefore the focus is on minimizing treatment side effects.

Section of Immunobiology
Prof. Dr. med. Stephan Thurau
Stephan.Thurau@med.uni-muenchen.de

Notes

New therapeutic modalities and monoclonals

Piergiorgio Neri, Italy

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Uveitis is one of the leading causes of visual impairment in ophthalmology. This disease can be divided into two sub-groups: non-infectious uveitis and infectious uveitis. In non-infectious uveitis, immunosuppressive therapy for severe, sight-threatening intraocular inflammation can be divided into two phases. The acute stage can be successfully controlled with use of pharmacologic agents such as corticosteroids. As soon as the acute phase is controlled, the reduction of the steroids dose is mandatory, since the long-term treatment with steroidal agents implicates a certain number of side effects, such as high blood pressure, high blood sugar, cataract and glaucoma. For such reasons, immunotherapy is often introduced, albeit the treating physician frequently shall balance side effects with a continued therapeutic response. An increased understanding of the mechanisms that result in non-infectious uveitis has made it possible to consider the use of other means to abrogate the ocular immune response.

Several immunosuppressants have been proposed for the control of sight-threatening uveitis **(Figure 1)**.

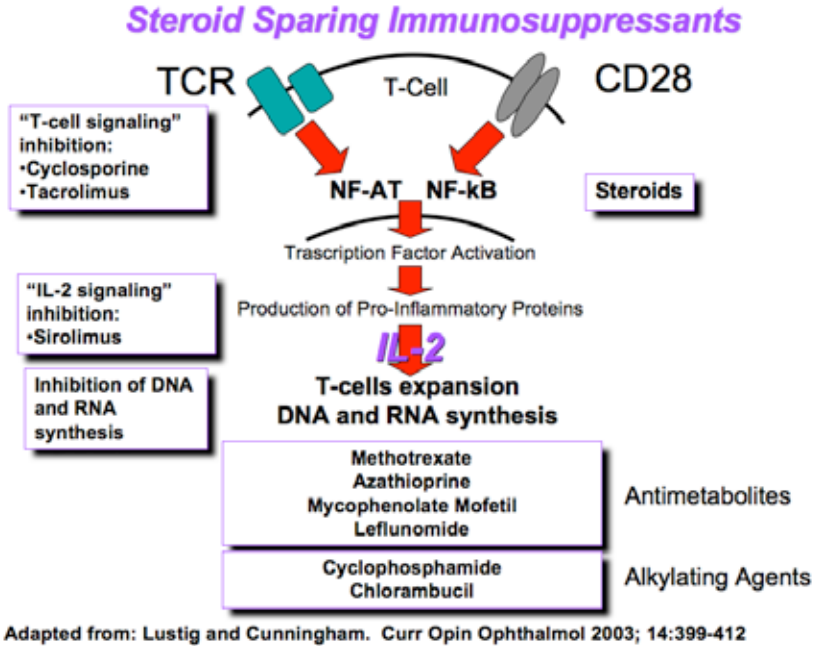

Figure 1

Beside the traditional immunesuppressive drugs, such as Azathioprine [1], Methotrexate [2], Cyclosporine A [3], and, more recently, FK506 [4], other immunosuppressives have been introduced for the management of sight-threatening non-infectious uveitis.
Mycophenolate Mofetil (MMF), another drug recently used for the control of uveitis, has shown promising results in controlling the uveal inflammation as well as in down-regulating the macular oedema [5].
More specifically, MMF is a reversible, noncompetitive, selective inhibitor of the de-novo pathway of purine synthesis, successfully used in the treatment of rheumatoid arthritis [6], pemphigus vugaris [7], and psoriasis [8]. Several reports have been published on its use for the control of uveitis: in 1998, Kilmartin and co-workers [9] reported a case series of patients, unresponsive to traditional immunosuppressants, successfully treated with MMF. More recently,
a larger number of cases has been presented in a retrospective study by Thorne et Al [10] and Siepmann et Al [11], confirming the results previously published.
The modern appraisal of the inflammatory mechanisms implicated in the uveitis pathogenesis has drived the modern approach towards a new category of drugs called biologics. This type of immunesuppressors represents a revolution in the management of such disease: biologics are highly specific molecules targeting inflammatory soluble mediators and represent the last frontier of ocular immunologic treatments **(Figure 2)**.

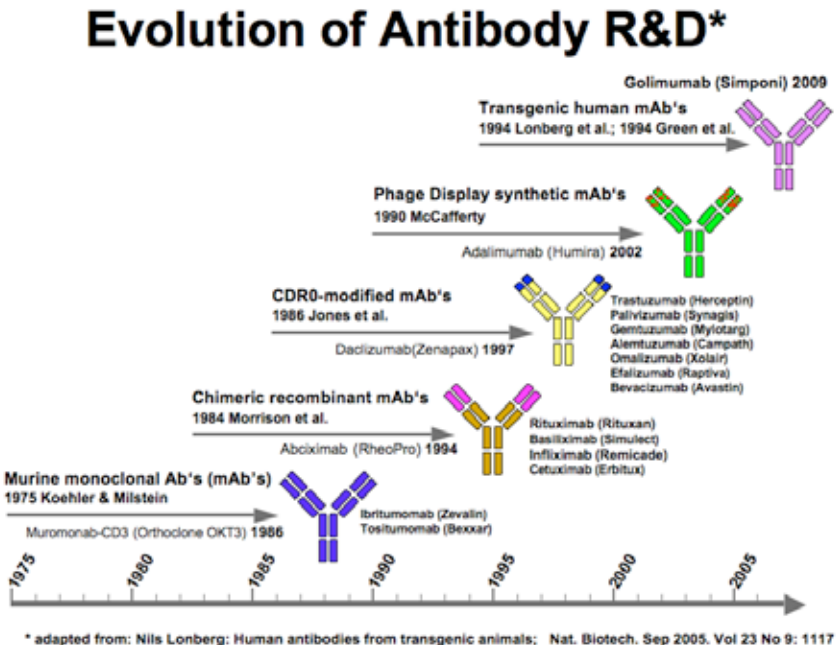

Figure 2

Albeit several biologic targets have been identified, anti-Tumor Necrosis Factor (TNF)-a blockers represent the most promising molecules used in the treatment of severe sightthreatening uveitis. TNF-α is a cytokinic key factor in the inflammatory cascade. TNF-α is generated and expressed by immune cells and binds to the corresponding TNF receptor (TNFR) family. This cytokine has affinity for two receptors, known as p55 or TNF-R1, and p75 or TNF-R2 [12,13] and the signal transduction induces and supports the inflammatory process in autoimmune reactions. TNF-α activates T-cells and macrophages, increasing the expression of endothelial adhesion molecules and pro-inflammatory cytokines. [12,14,15]

TNF-α plays a key role in the pathogenesis of many inflammatory diseases: TNF-α has been detected in all the tissues affected by an active inflammation, such as the synovial fluid in patients with rheumatoid arthritis (RA) or psoriasis arthritis (PsA), as well as the bowel mucosa in Crohn's disease or ulcerative colitis and the eye during acute uveitis.

Non-infectious intermediate, posterior, and pan-uveitis [16,17] are antigen-specific CD4 T-cell–mediated autoimmune diseases. In these diseases, TNF-α represents one of the most important amplifying factors in the inflammatory reaction [18-20]: in case of uveitis, TNF-α is present at high concentration levels both in the aqueous humour and in the serum [21-25], similarly to RA [26].

The first commercially available anti-TNF-α drug was infliximab, a chimeric immunoglobulin G (IgG) 1 monoclonal antibody containing human and murine portions targeting TNF-α [27].

Concomitantly, etanercept [28] a dimeric fusion protein consisting of two extra-cellular domains of the human p75 TNF-α receptor linked to the Fc portion of human IgG has in the same time become available [28]. Etanercept is now actually not recommended in inflammatory diseases associated with uveitis, because it was active in exacerbating uveitis and even in producing uveitis "ex novo" [29].

Dick et al. [30] showed that TNF-α inhibition with a p55 TNF-α receptor fusion protein (TNFr-Ig) reduces interferon (IFN)-α and elevates interleukin (IL)-4 production, suggesting that this mechanism may induce the deviation of the immune response from a Th1 response towards a Th2 reaction with concomitant clinical improvement.

Adalimumab, a recombinant IgG1 monoclonal antibody targeting TNF-α, showed its efficacy both as a mono-therapy and in combination with other disease-modifying anti-rheumatic drugs (DMARDs), with a good safety and efficacy profile in inflammatory rheumo-arthropaties of different aethiology. Adalimumab has been proven to be effective in adult patients for the treatment of RA [31], ankylosing spondylitis (AS) [32] and PsA [33], by reducing symptoms of joint involvement and by inhibiting the progression of structural damage, typical of these immune-mediated diseases.

Unlike infliximab and other biologic agents which have to be administered intravenously, adalimumab has the technical advantage of a subcutaneous (SQ) administration.

Some questions are emerging with the introduction in ophthalmic therapy of adalimumab, such as when to begin therapy, at what dosage and how long [34]. Until now adalimumab has mostly been given in case of failure of other anti-TNF-α agents, or because of its convenient administration route.

Albeit adalimumab is produced by recombinant deoxyribonucleic acid (DNA) technology, called

"phage display", and is classified as a fully humanized antibody, the humanization of such monoclonal antibody is almost complete, albeit not total. Recently, another monoclonal antibody has been introduced for the treatment of RA: golimumab [35]. The real innovation of such molecule is represented by its fully humanized structure, due to the transgenic technology: golimumab derives from a Sp2/0 cell line that has been transfected with an expression plasmid containing the genes encoding the heavy and light chains. Although this new drug presents fascinating aspects, there is no report on uveitis to date. One of the key points regarding monoclonal antibodies is represented by the clinical failure in controlling the inflammatory process. Failure of anti-TNFα agents such as infliximab can be twofold: either poor response when starting the therapy ("primary failure") or progressive decrease of efficacy because of the production of patient antibody reaction to the molecule used for treatment ("secondary failure").

Similar to systemic diseases, the switching from a certain biologic agent to another has been effective [36] in maintaining inactive immune-mediated uveitis, even though this preliminary evidence has to be validated by further trials.

A particular attention should be paid to a very interesting and promising drug, which is playing an important role in the management of severe sight-threatening uveitis: Interferon Alpha (INF-α). IFN-α is a naturally occurring cytokine secreted in response to viral infections, primarily by plasmacytoid dendritic cells. Simplistically, IFN-α is proposed as the primary pathogenic cytokine in 'systemic' autoimmune diseases, whereas TNF-α is believed to be the more pathogenic cytokine in organ-specific autoimmune diseases. The recent literature reveals many similarities between TNF-α blockers and IFN-α therapies for uveitis. Both agents have a rapid effect on intraocular inflammation and achieve control of uveitis in a high percentage of patients that have failed to respond to traditional second-line immunosuppressants. Recombinant human IFN-α2a and IFN-α2b have both been used to treat posterior uveitis successfully, with the majority of studies using IFN-α2a. IFN-α [37] is given by subcutaneous injection, commonly starting with high dose daily injections with a subsequent taper to low dose intermittent injections. It is standard procedure to discontinue second-line immunosuppressants prior to IFN-α therapy, and many ophthalmologists also taper corticosteroids to as low a dose as possible. In summary, new immunesuppressive treatments and biologic therapies have increased the treatment options for sight-threatening uveitis. Despite experimental rationale, the lack of evidence from randomized controlled studies limits our understanding of when to commence therapy, which agent to choose and how long to continue treatment. In addition, the high cost and potential side effects of the biologic drugs have limited their current use to uveitis refractory to traditional immunosuppression.

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Piergiorgio Neri, BMedSc, MD(Hons), PhD, Assistant Professor of Ophthalmology
The Eye Clinic, Polytechnic University of Marche, Ancona, Italy
Uveitis

Notes

Surgical management

Marc de Smet, Switzerland

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Introduction:

Manipulation of the posterior segment will be required in the management of patients with uveitis to help solve diagnostic dilemmas, prevent or treat complications of uveitis, treat concurrent posterior segment pathologies, or provide specific therapies which re-quire access to the posterior pole.

As with all surgeries in inflammatory ocular diseases of non infectious origin, surgery should be delayed whenever possible until the inflammation is under control for 3 or more months. Patients should have their immunosuppression increased prior to surgery. Regimens designed for cataract surgery are usually adequate, except that non steroi-dals can be limited to topical use. At the completion of surgery, patients should be given appropriate local (peri-ocular or intraocular) immunosuppression. In most patients this will consist in the use of a steroid based compound unless the patient is a known severe steroid responder.

For patients with an infectious cause for their ocular inflammation, the course will de-pend on the severity of the ocular inflammation and the degree of tissue destruction. In general, the prognosis is poor during active disease. Such cases should be restricted to competent well trained VR surgeons, and surgery should be aggressive enough to not only remedy the immediate ocular problem, but prevent future complications. Treatment with anti-infective agents on the basis of a presumed diagnosis is often indicated par-ticularly in cases where retinal necrosis is suspected, as time is of the essence if vision is to be preserved.

VR for diagnostic indications:

The least invasive approach likely to yield a diagnosis should be chosen. Surgery should only be attempted after thorough discussion with the specialists involved in proc-essing the tissue (pathologist, cytopathologist, hematologist, infectious disease special-ist). They should be aware of the small nature of the tissue sample and be aware of your primary differential diagnosis.

In the presence of severe vitritis, a biopsy via a 25G trocar may be all that is necessary. A sample of 1 mL can be taken without much risk to the eye. For involvement primarily in the retina, subretinal space or choroid, one may need to obtain a retinal or retino-choroidal biopsy. As there is more risk to the eye, this approach should be limited to cases where there is sight threatening disease and where the course of treatment would be altered by the results of the biopsy. Generally it should only be undertaken when the results of less invasive approach are negative. In all cases, the sample obtained should be used to gain maximum yield. Cytology can give you an idea of cell type, - FACS analysis the distribution of particular cell popula-tions (for example in lymphoma or cancer), - microbiology the presence of an infection either by direct culture or by PCR, - a Goldman Witmer quotient on vitreous fluid the type of antibodies being generated intraocularly. A combination of techniques can help to improve the diagnostic yield: a chronic endophthalmitis is generally characterized by the presence of macrophages rather than polymorphonuclear cells. (1-6)

Vitrectomy for macular edema and macular traction syndromes:

Vitrectomy has long been considered an approach to reduce the degree of intraocular inflammation and reduce the need for immunosuppression. This is particularly true in cases where the disease is not particularly active or is due to intermediate uveitis (in-cluding relatively mild forms of pars planitis). Removal of the vitreous reduces the bur-den of inflammatory mediators and there is often a period of time during which ocular attacks are less frequent or severe. However, they can recur if immunosuppression is tapered too drastically, and it can manifest itself with severe hypotony when cyclitis is present.

Removal of vitreous traction on the fovea will lead to improvement in macular edema. However, the degree and permanence of the result will depend on the degree of struc-tural damage to the retina and the intactness of the microvasculature around the foveal avascular zone. (7-12)

Vitrectomy for retinal fibrosis (ERM, hypotony):

Epiretinal membrane formation is not uncommon in uveitis patients and can develop fol-lowing previous vitrectomy or following vitritis secondary to infections such as toxoplas-mosis. Epiretinal membranes in this setting are often multi-layered and may require re-peat staining of the affected area to be removed. One should take particular care in children where such membranes can develop into a gliotic scar. These should be ad-dressed surgically before such a stage develops. Hypotony results for incomplete vitrectomy carried out in the anterior portion of the vitre-ous cavity. If a vitrectomy is carried out in an inflamed eye, it should be as complete as is feasible. It often requires a combined vitrectomy and cataract extraction if one is avoid leaving excessive vitreous anteriorly which will condense on the posterior surface of the iris and over the ciliary processes. In cases of hypotony with preservation of ciliary body function, this tissue needs to be removed from the pars plicata over an extensive area if the visual function and the eye are to be preserved. (13)

Management of retinal detachments in uveitis:

Retinal detachments are relatively rare in uveitis patients occuring in about 1% of pa-tients. They are obviously more common in infections, particularly those associated with retinal necrosis (ARN, CMV). The more extensive the necrosis, the more likely is a de-tachment. The latter oc-curs as the vitreous detaches from the posterior pole. In most cases of ARN that occupy 2 or more quadrants, a prophylactic vitrectomy should be considered particularly in cases with an intact vitreous.

The prognosis of retinal detachments in uveitis patients depends on the severity of in-flammation. In a quiescent eye, the prognosis should be no different from any other de-tachment surgery. In eyes with active inflammation, prognosis is usually poor. One should minimize inflammation (laser rather than cryo, and vitrectomy rather than encir-clement). Liberal use of silicone oil is also ad-vised in active inflammation as the oil will also act as an “insulator”, preventing membranes from developing which could act as a bridge between opposite sides of the vitreous cavity.

Note that in an inflammatory setting, most detachments are not rhegmatogenous but serous in origin. A good indirect ophthalmoscopic examination is a must preferrably with indentation. (14,15)

Therapeutics:

Implantable devices to treat infection or inflammation is becoming more frequent. The retisert implant placed through the pars plana will provide control of inflammation for up to 3 years but at a considerable cost (to the patient) and to the eye (assured cataract development and 40% glaucoma). Ganciclovir implant - can be used to treat locally se-vere CMV retinitis uncontrolled by systemic or intraocular anti-viral agents.

Non sutured slow release biodegradable or non biodegradable devices can also be used to control moderately severe uveitis and or macular edema. In the future, vitreolytic agents may help to release vitreo-retinal traction and thereby reduce the risk of macular edema. This approach is currently under clinical investigation.

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Marc D. de Smet, MDCM, PhD, FRCSC, FRCOphth
Professor of Ophthalmology, University of Amsterdam
Director, Retina and Inflammation Unit, Clinique de Montchoisi, Lausanne, Switzerland
mddesmet1@mac.com

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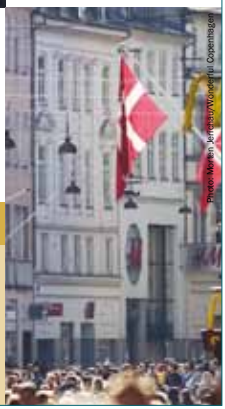

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PROGRAMME EUPO 2011

Friday, June 3

Uveitis: the basics and beyond

- 08.30 - 10.00 **Section 1: Basic concepts**
- 10.30 - 12.10 **Section 2: Anterior segment**
- 13.20 - 14.40 **Section 3: Posterior uveitis 1**
- 14.40 - 15.20 **Section 4: Posterior uveitis 2**
- 16.20 - 17.40 **Section 5: Therapy**
- 18.15 EUPO Party

Saturday, June 4

Glaucoma: from scientific evidence to clinical practice

- 08.15 - 09.45 **Section 1: Diagnosis and fate of POAG**
- 10.15 - 14.15 **SOE Programme**
- 14.30 - 16.00 **Section 2: Management 1**
- 16.30 - 18.00 **Section 3: Management 2**