European University Professors of Ophthalmology

EUPO 2015

Course on

UVEITIS
GLAUCOMA

June 5-6, 2015
Vienna, Austria

In conjunction with SOE 2015

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EUPO 2015

Uveitis & Glaucoma

European University Professors of Ophthalmology

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UVEITIS

Organised by Carlos Pavesio

GLAUCOMA

Organised by the European Glaucoma Society

Course coordinator: Carlo Traverso

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The sequence of the EUPO courses

2015	Vienna (SOE)	Uveitis & Glaucoma
2014	Nice (EVER)	Retina
2013	Copenhagen (SOE)	Cornea, Conjunctiva and Refractive Surgery
2012	Leuven	Neuro-ophthalmology and strabismus
2011	Geneva (SOE)	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	First EUPO course

Carlos Pavésio, Uveitis EUPO course organizer

Dear colleagues,

It is a great pleasure for us to welcome you to Vienna, host of the 2015 Course of the European Professors of Ophthalmology (EUPO). This year, Uveitis is one of the focuses of the course and this comes at the time when there has been growing interest in this field with many new developments, both in terms of diagnosis and treatment.

I am thankful to all my colleagues and friends who have agreed to contribute to this year's course. The course will cover basic sciences and clinical aspects, and will bring practical guidance from experts who have agreed to join us for what promises to be an exceptional day. 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 represent an excellent update of the subject and will provide invaluable guidance for your daily practice.

I hope you will all enjoy the course and the beautiful and friendly city of Vienna.

Mr Carlos Pavesio

Uveitis EUPO Course Organizer

available on www.eupo.eu

EUPO 2006
Retina

EUPO 2007
Uveitis

EUPO 2008
Neuro-Ophthalmology and Strabismus

EUPO 2009
Cornea, Conjunctiva and Refractive surgery

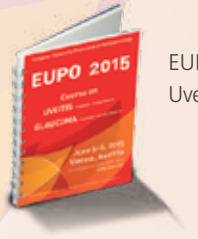
EUPO 2010
Retina

EUPO 2011
Uveitis and Glaucoma

EUPO 2012
Neuro-ophthalmology and Strabismus

EUPO 2013
Cornea, Conjunctiva and Refractive Surgery

EUPO 2014
Retina



EUPO 2015
Uveitis & Glaucoma

European University Professors of Ophthalmology

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Programme EUPO 2015

Friday June 5, 2015
UVEITIS: The basics and beyond

MCQ answers - pages 193-198

Programme EUPO 2015

Saturday June 6, 2015
GLAUCOMA

• Session 1: Surgical management

- Getting prepared
  J SALMON, United Kingdom
- Getting the surgery right
  I STALMANS, Belgium
- Handling postoperative troubles
  C TRAVERSO, Italy

• Session 2: Monitoring and Treatment decisions

- Zen or Maniak? How frequently should we monitor and the relevance of RoP
  J THYGESEN, Denmark
- To treat or not to treat, that's the question for OHT and glaucoma suspects
  N PFEIFFER, Germany
- Medical treatment or surgery, that's the question. A choice of treatment in glaucoma based on RoP and other factors
  Stefano GANDOLFI, Italy

• Session 3: Diagnosis (and impact on Quality of Life)

- Tonometry Today
  T HOMMER, Austria
- Pearls of Perimetry
  A HEIJL, Sweden
- Structure made Simple
  D GARWAY-HEATH, United Kingdom

Networking Reception

A networking reception will take place in the ACV on Saturday, 6 June between 18.00 – 19.00.

Certificate of Attendance EUPO 2015

Certificate on Attendance will be sent by email to all EUPO delegates after the SOE 2015 Congress.

CME credits EUPO 2015

CME is included in the overall SOE Programme.

MCQ's

What is the role of T helper cells?

- ❑ To lyse pathogens
- ❑ To help to suppress autoimmune responses
- ❑ To help B cells and cytotoxic T cells
- ❑ To secrete antibodies and histamine

What are pattern recognition receptors?

- ❑ Antigen-receptors of T lymphocytes specific for peptides
- ❑ Special molecules on the surface of bacteria and viruses
- ❑ Receptors on macrophages to bind antibodies complexed with antigen
- ❑ Receptors on innate immune cells recognizing pathogens or dead cells

What is necessary to maintain the immune privilege of the eye?

- ❑ Spleen and eyes
- ❑ Autoreactive T cells
- ❑ The blood-brain-barrier
- ❑ Insulin

The immune system consists of an „innate“ (macrophages, dendritic cells, granulocytes, NK cells, mast cells, complement system) and an „adaptive“ (T and B cells, antibody responses) arm. The innate immune system is alerted by certain molecular pattern of bacteria and viruses and even by own cells being “unwell” or dying and it quickly reacts (within minutes to hours), either removing the invaders by itself, and/or by mobilizing the adap-tive immune system via antigen presentation and secretion of mediators (cytokines, chemokines) to inform the T and B cells about the situation in the body. The latter cause a pathogen-specific, “tailored” and more differentiat-ed immune defense response, which needs more time to develop (several days).

The innate immune recognition uses „pattern recognition receptors“ (PRR), which are located on the cell surface and within the cell. These PRR (e.g. Toll-like receptors TLR, NOD-like receptors NLRs) induce the production of inflammatory cytokines like interferons, IL-1 and IL-12 in the pathogen-sensing cell. Some PRR are forming complexes with other cytoplasmic molecules, resulting in „inflammasomes“ that activate IL-1 and IL-12. These cytokines activate the B and T cells of the adaptive arm of the immune system.

Mutations of the NLR intracellular PRR can cause in an imbalance and reduced or overshooting inflammation even without an infectious stimulus. The consequences can be increased susceptibility to infections, „autoin-flammation“ and/or various diseases including autoimmunity, cancers and even abnormal embryonic develop-ment. The acute HLA-B27-associated anterior uveitis and Behçet’s disease are thought to be triggered by autoin-flammation.

B cells produce antibodies and also present antigen to T cells to ask for their help, which is needed e.g. for the isotype switch of antibodies (changing from IgM to IgGs and IgE). While B cells can recognize very complex antigens (proteins, carbohydrates, nucleic acids, nitrophenyl etc.) with their receptors (= membrane-anchored antibodies), T cells only recognize peptides “processed” from proteins by antigen-presenting cells (“profession-al” APC: dendritic cells, macrophages or B cells) presented on HLA antigens. CD8+ T cells have mainly cyto-toxic functions (but some are also regulatory cells), while the CD4+ T cell population includes the T helper cells and also a regulatory T cell population (CD4+CD25+). The CD4+ T cells provide help for other T cells (e.g. for CD8+ cytotoxic T cells) and for B cells, enhancing their antibody production and isotype switch. T cell types can be distinguished by the pattern of the cytokines they secrete: while Th1 cells secrete interleukin-2 (IL-2), interferon-gamma (IFN-g) and tumor necrosis factor-alpha (TNF-α), the main

cytokine produced by Th2 cells is IL-4. Th17 cells produce IL-17 and TNF-α, they are e.g. needed for the defense against fungal infections. All T cell types also play roles in various autoimmune diseases including uveitis.

Autoimmune uveitis is mediated by T-helper cells, presumably of the Th1 or Th17 type. When these cells recog-nize antigen in the eye, they recruit inflammatory cells (macrophages, granulocytes), which can destroy the in-traocular tissues.

To preserve the eyes from destructions by the immune system, mechanisms have developed that prevent inva-sion of non-activated lymphocytes and potentially dreadful immune components. The so-called "immune privi-lege" is mediated by the blood-retina-barrier and "ACAID" (anterior chamber-associated immune deviation). In very rare cases sympathetic ophthalmia can result from the destruction of the blood-retina-barrier (e.g. by pene-trating injury, tumors with invasive growth) enable the invasion of non-activated T cells for in situ activation to ocular antigens (injury of one eye leads to autoimmune attack of the other eye).

Activated leucocytes can overcome the blood-retina-barrier as well as ACAID. They are enabled to penetrate the BRB and are not hampered by the suppressive factors in the eye. However, they have to be activated specifically for intraocular antigens, which are usually 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 a different antigen in the eye that, however, 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 derived from environmental antigens such as pathogens (e.g. rotavirus, mycobacteria) or even from nutritional antigens (e.g. casein from bovine milk).

Destruction of tissues caused by inflammatory cells of the innate immune system releases new autoantigens, which can activate new cells (T and B cells) of the adaptive immune system; they will then recruit inflammatory cells again, resulting in a „vicious cycle" that has to be interrupted by suitable therapeutic interventions.

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NOTES

MCQ's

In which clinical situation is the PCR method useful?

- ❑ Detection of infectious agent from ocular fluid in quiescent uveitis
- ❑ Prove of monoclonality of lymphoma from vitrectomy specimen
- ❑ Screening for syphilis infection
- ❑ Detection of flare in the anterior chamber

Which statement about the Goldman-Whitmer-coefficient is correct?

- ❑ Titers from ocular specimens are compared to titers from serum
- ❑ Measurements of total IgG in the specimens is not required.
- ❑ Comparison of specific IgG to total IgG in ocular and serum.
- ❑ Increase of antibody titer within 4 weeks

In which situation is serologic testing most useful for the diagnosis of uveitis?

- ❑ HSV-serology in suspected acute retinal necrosis
- ❑ Rubella serology in Fuchs' uveitis
- ❑ Toxoplasma serology in retinal vasculitis
- ❑ Syphilis test in unclear uveitis

In the diagnosis of uveitis different molecular techniques are used.

Detection of antibodies (serology)

Antibodies directed against different infectious agents can be detected in serum and intraocular samples. These antibodies indicate an immune response to an infectious agent. Since antibody production requires at least 2 weeks, this diagnostic approach is more suitable for chronic conditions and not for acute disease. Antibodies may remain in the circulation for decades even if the infection had been cleared or treated successfully. Antibody isotypes can indicate whether the infection is primary (IgM) or longer lasting (IgG), the antbody titer indicates latent (lower titers) or reactivated infection (high titers of IgG).

Typical indications include antibody testing for syphilis, toxoplasmosis, lyme disease or bartonellosis using serum. Serological testing for other infectious agents like the viruses of the herpes family is not of any diagnostic value because of the high prevalence of antibodies in healthy as well as uveitis patients.

Antibody detection in intraocular samples for comparison with serum titers (Goldman-Whitmer-coefficient) is of high diagnostic value, but limited to a small numbers of tests due to sample size, if this test is availabel at all.

Polymerase chain reaction (PCR)

PCR detects RNA or DNA by amplifying genes specific for a certain infectious agent. Since PCR directly probes an presence of an infectious agent, it is suitable for acute diseases. In contrast to serology PCR often turns negative after initiation of treatment or during the course of disease, even if the infection is not completely cleared and ongoing.

Typical indications include samples from fluids like anterior chamber taps, vitreous, or tissues like cornea and others in suspected infections with herpes viruses and toxoplasma gondii.

PCR can also be applied to prove monoclonality of B- or T-cell lymphomas in retinal or iris biopsies as well as vitrectomy specimens.

It is the routine technique for HLA-typing using lymphocytes from peripheral blood.

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MCQ's

The following statements about the fluorescein sodium molecule and fluorescein angiography are correct except one

- ❑ Injection of fluorescein can be lethal in some rare instances
- ❑ Fluorescein is the method of choice to study lesions of the retinal pigment epithelium
- ❑ A patient with eye inflammation suspected of having Behçet's disease should have a fluorescein angiography performed (absolute indication)
- ❑ The fluorescein molecule is producing fluorescence in the visible light spectrum is therefore suitable for the analysis of choroidal structures

The following propositions are true for the ICG molecule or ICG angiography except one

- ❑ ICG forms a large macromolecular complex with proteins and therefore does not extrude from capillaries unless they are fenestrated with large pores such as the choriocapillaris
- ❑ ICG is particularly well indicated to analyse the RPE because it emits fluorescence in the infrared that can cross the optic barrier of the retinal pigment epithelium
- ❑ ICGA is particularly useful in diseases of the choriocapillaris such as MEWDS (multiple evanescent white dot syndrome), APMPPE (acute posterior multifocal placoid pigment epitheliopathy and multifocal choroiditis
- ❑ In a large proportion of cases indocyanine green angiography shows occult lesions that could not have been detected otherwise

The following propositions are true for angiography and OCT in inflammatory diseases except one

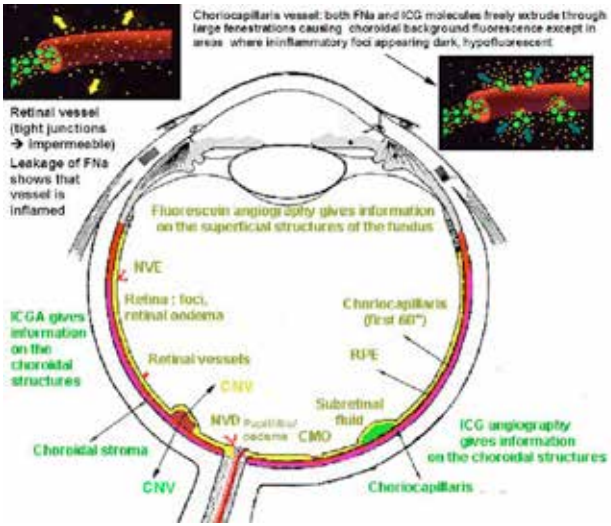
- ❑ Fluorescein angiography is necessary to analyse the retinal pigment epithelium
- ❑ Fluorescein angiography is absolutely necessary to investigate inflammation of retinal vessels
- ❑ Indocyanine green angiography (ICGA) is required to analyse choroidal structures
- ❑ Indocyanine green angiography is rarely used because inflammation of the choroid is rare
- ❑ OCT cannot be used to follow stromal choroiditis entities such as VKH disease
- ❑ OCT is giving realtime information on the macula in inflammatory diseases

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 retro-iridal vitreous is sometimes important. These structures are not readily accessible with routine examination methods. Evaluation of the retro-lenticular and retro-iridal 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 retro-iridal space.

5. Fundus autofluorescence (FAF) in uveitis

Autofluorescence has become one of the centers of interest in fundus imaging since the confocal scanning laser opththalmoscope (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 containing 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 (FA) 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 damage, 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 chorio-retinal 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 photo-shots 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 45o to the antero-posterior axis. At an angle of 90o degrees to the incoming laser beam (45o to the antero-posterior axis) a photomultiplier-photodetector 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 photo-multiplier 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

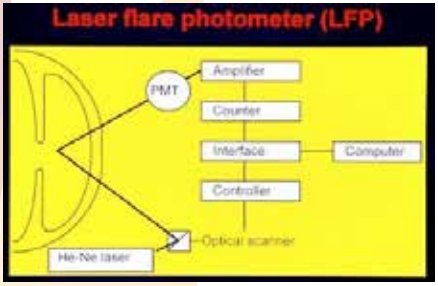
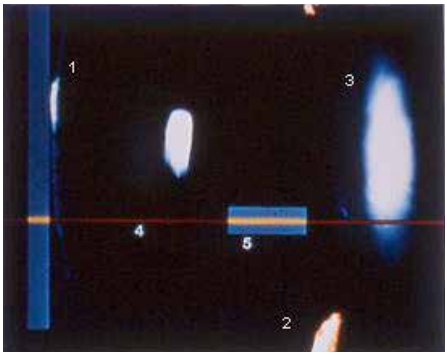


Figure LFP-2. Laser flare photometry : observer's view during measurement procedure. The measuring window has to be placed in the darkest part of the anterior chamber at equal distance from the cornea and the crystalline lens anterior-posteriorily and between the middle and inferior third along the vertical axis. During the measurement sequence, the beam moves up and down from above the window, going through the measurement window and beyond. The photon counts above and below the window will account for the background light which will be deduced from 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 auto-refraction, 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 glaucoma 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 centres 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 influential 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 diffused 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 long last this technology is however going to be part of the standard equipment of uveitis centres.

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2. Indocyanine green angiography (ICGA)

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2.2. Herbort CP, Mantovani A, Papadia M. Use of indocyanine green angiography in uveitis. Int Ophthalmol Clin 2012; 52:13-31.

3. Optical Coherence Tomography (OCT)

3.1. Onal S, Tugal-Tutkun I, Neri P, Herbort CP. Optical coherence tomography imaging in uveitis. Int Ophthalmol 2014; 34: 401-435.

4.Ultrasound biomicroscopy (UBM)

4.1. Tran VT, LeHoang P, Herbort CP. Value of high-frequency ultrasound biomicroscopy in uveitis. Eye (Lond) 2001; 15:23-30.

5. Fundus autofluorescence (FAF)

5.1. Reznicek L, et al. Systematic analysis of wide-field fundus autofluorescence (FAF) imaging in posterior uveitis. Curr Eye Res 2014; 39:164-171.

6. Laser flare photometry (LFP)

6.1. Tugal-Tutkun I, Herbort CP. Laser flare photometry: a non-invasive, objective, and quantitative method to measure intraocular inflammation. Int Ophthalmol 2010; 30:453-64.

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MCQ's

The most sensitive ERG parameter in birdshot chorioretinopathy is:

- ❑ The dim flash dark-adapted (rod specific) ERG;
- ❑ The bright flash dark-adapted ERG;
- ❑ The photopic 30Hz flicker ERG
- ❑ The pattern ERG

Melanoma associated retinopathy is associated with:

- ❑ Normal ERGs;
- ❑ ERG extinction;
- ❑ ERG abnormalities confined to the rod-system;
- ❑ Global loss of retinal On-pathway function

AZOOR is usually associated with:

- ❑ Normal ERGs;
- ❑ Delayed photopic 30Hz flicker ERG;
- ❑ An electronegative ERG;
- ❑ Rod-system derived ERGs more abnormal then cone-system derived ERGs

The presentation will address the roles of electrophysiological assessment in inflammatory disease. After a short introduction to the tests, their origins, and the significance of abnormalities, a case-based approach will be used to demonstrate the two main uses of electrophysiology: diagnosis, and objective monitoring of disease severity and the efficacy of therapeutic intervention. Disorders shown will include birdshot chorioretinopathy, AZOOR and auto-immune mediated retinopathy.

Prof. Graham Holder
London, United Kingdom

Anterior uveitis: general considerations

Nicholas Jones, United Kingdom

05

MCQ's

Select one most appropriate answer from the following:

- ❑ Oral steroids should never be used to treat anterior uveitis
- ❑ Hypopyon containing blood usually indicates Fuchs' heterochromic uveitis
- ❑ Raised intraocular pressure is typical of anterior uveitis related to HLA-B27
- ❑ The hypopyon in HLA-B27 related uveitis is typically mobile
- ❑ Iris nodules are most commonly seen in eyes with Fuchs' heterochromic uveitis

Answer "true" or "false" to each of these statements about infective anterior uveitis:

❑ true ❑ false Cytomegalovirus can cause anterior uveitis without retinitis, even in the immunocompetent

❑ true ❑ false Any treated intraocular infection can be followed by chronic non-infective anterior uveitis

❑ true ❑ false Tuberculosis never causes anterior uveitis alone, without posterior segment involvement

❑ true ❑ false Chronic anterior uveitis with sectorial iris atrophy is typical of HSV-1

❑ true ❑ false If syphilis involves the anterior segment, inflammation is always granulomatous in appearance

Answer "true" or "false": when managing severe acute anterior uveitis:

❑ true ❑ false A positive syphilis ELISA with an RPR of 1:4 indicates active syphilis

❑ true ❑ false Phenylephrine should not be used to dilate the pupil

❑ true ❑ false Sub-conjunctival steroid injection is ineffective if the patients is using hourly prednisolone acetate

❑ true ❑ false If the posterior pole can be seen to be normal, there will be no retinitis

❑ true ❑ false Any posterior synechiae should be broken on the first day of presentation if possible

Anterior Uveitis

General Considerations

Nicholas Jones

MREH200 1814-2014

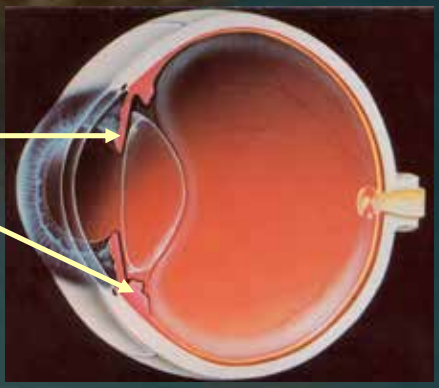
Manchester Uveitis Clinic
The Royal Eye Hospital
Manchester, UK

Disclosure Statement of financial interest

- I, Nicholas Jones, DO NOT have a financial interest/arrangement or affiliation with one or more organisations which could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation

Anterior means anterior only

IUSG classification:
Anterior uveitis = Iris
& pars plicata



AU Presentations: A diagnostic approach

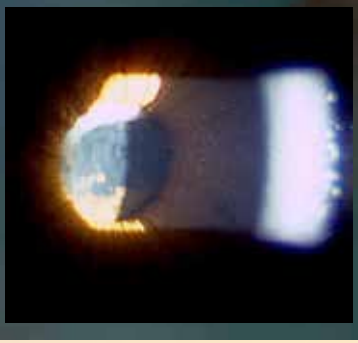
- 1. Acute unilateral non-granulomatous AU
  - (60-70% of all new patients)
- 2. Bilateral or granulomatous AU
  - (10-20%)
- 3. Subacute or chronic AU with unusual features
  - (10%)

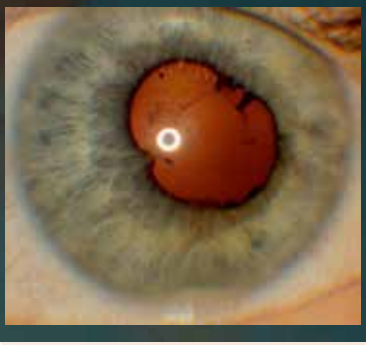
Acute unilateral non-granulomatous AU – investigate ?

- 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

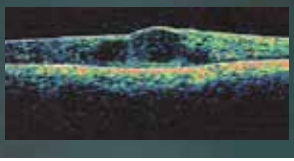
- Unilateral, photophobia, ciliary congestion
- Posterior synechiae, low IOP, exudate





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/rediscovered treatment skills

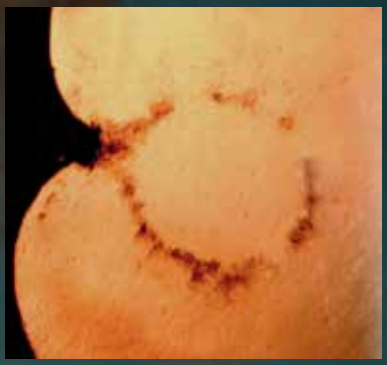
- Duke-Elder (1966):
- "each attack leaves its mark, producing irreversible changes, and the end-result is indistinguishable from an acute attack of destructive severity which terminates in phthisis."
- "Prompt *treatment* is therefore the vital factor in the prognosis – rest, full atropinisation at 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 (atropine, procaine, adrenaline)
- 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 ?

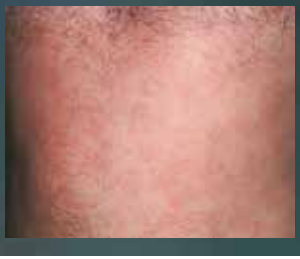
- History
  - Known medical diagnosis, treatment - detailed
  - Ask: arthropathy, bowel, chest, skin, STD, recent illness, travel
- Investigations
  - CXR - Chest CT if doubtful signs
  - ACE
  - FBC, ESR, CRP
  - Syphilis serology
  - Consider tuberculin testing if suspicious

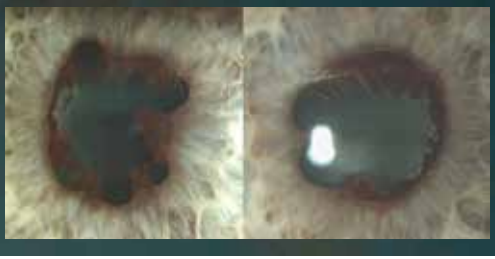
Don’t miss infective AU

- 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

Cytomegalovirus anterior uveitis

- Immunocompeten
- Unilateral, chroni
- Often hypertensiv
- Sometimes pigme
- Sometimes iris atr
- Oral valganciclov oral valaciclovir)
- ? intraocular ganciclovir

Subacute/chronic symptoms with peculiar features – investigate ?

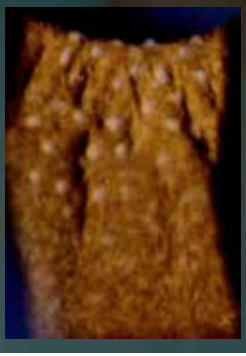
- Consider uveitis syndromes including:
  - Fuchs' heterochromic uveitis
  - Posner-Schlossman syndrome
  - Herpes simplex uveitis
  - Phakogenic uveitis
  - Non-malignant masquerades:
    - Ocular ischaemia
    - RD, Schwartz syndrome, ghost cell glaucoma
  - Malignant masquerades (very rare)

Fuchs' heterochromic uveitis

- KP morphology
- Corneal plaques

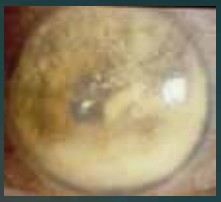
Fuchs' heterochromic uveitis

- 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



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NOTES

MCQ's

The differential diagnosis of JIA associated uveitis does not include:

- ❑ HSV anterior uveitis.
- ❑ Other rheumatic disorders.
- ❑ Uveitis masquerade syndromes.
- ❑ Toxoplasmosis retinochoroiditis.

Uveitis risk factors and uveitis screening in JIA patients. What is correct?

- ❑ Uveitis mostly occurs in rheumatoid-factor positive patients.
- ❑ In oligoarthritis patients, uveitis onset is most frequent at ≥ 10 years of age.
- ❑ Major risk factors for uveitis manifestation are oligoarthritis, young age at arthritis onset, short duration of disease and ANA-positivity.
- ❑ Uveitis screening at 12-months intervals is sufficient in high-risk patients.

Therapy of oligoarthritis associated uveitis. What is correct?

- ❑ Inflammation can always be managed with topical steroids.
- ❑ Severe cases often require immunosuppressives or biologicals.
- ❑ IOL-implantation is always contraindicated.
- ❑ Glaucoma can mostly be managed with topical glaucoma medication.

Prevalence and differential diagnosis. The uveitis prevalence in children and adolescents up to the 16th year of life in Europe is estimated to be 25–30/100 000. The disease spectrum in children includes infections as well as uveitis in inflammatory-rheumatic disorder and uveitis masquerade syndromes. Careful etiologic investigation is therefore required. This is based on the anatomical form of the uveitis (anterior uveitis), the medical history, and the suspected clinical diagnosis. The most common disorder underlying uveitis in children is juvenile idiopathic arthritis (JIA). JIA associated uveitis is estimated to have a poor prognosis and has a high rate of complications. It is associated with far-reaching consequences for patients and substantial socioeconomic burdens.

Risk factors In patients with early-onset arthritis, the risk of uveitis is strikingly increased. The mean age at initial manifestation of JIA is between six and seven years, whereas children who additionally develop uveitis develop JIA earlier: in the fourth and fifth years of life. JIA associated uveitis is more commonly observed in girls (75–80%). The cumulative incidence of uveitis is significantly higher in ANA-positive patients than in ANA-negative patients.

Clinical presentation: JIA is typically accompanied by recurrent, non-granulomatous, anterior uveitis. Characteristically, the onset of uveitis and subsequent episodes remain unnoticed by the affected children and their parents in more than 85% of cases. This form of uveitis therefore entails a higher risk of delayed diagnosis than acute uveitis. Even severe intraocular inflammation usually remains asymptomatic, without any externally visible irritations, and can be detected only by an ophthalmologist using a slit lamp.

Complications: Posterior synechiae develop in cases of high inflammatory activity as a result of fibrin exudation. They are a common complication and accelerate opacification of the lens. Cataract formation as the most common complication impairing visual acuity (19–81%) is furthermore advanced by the chronic inflammation and intensive topical and/or systemic corticosteroid treatment. Additionally, ocular hypertension (≥ 22 mm Hg) and secondary glaucoma—with optic nerve damage and visual field defect—are typical and common complications (10–40%). OCT can detect inflammatory macular edema far earlier than had been assumed previously. Severe inflammation in the ciliary body may be followed by inflammatory infiltration of the vitreous, affecting visual acuity, ocular hypotension, and atrophy of the eye (phthisis bulbi). If opacification of the optical media develops at a pre-school age there is a risk of amblyopia. 20–45% of patients have complications even at their initial diagnosis of uveitis.

The risk of complications endangering visual acuity is lower in JIA patients with symptomatic uveitis (<15% of cases, 40% HLA-B27 positive). Such children have enthesitis-related arthritis in most cases, which manifests at an older school age and affects primarily boys. Typically, this form of arthritis is accompanied by unilateral acute anterior uveitis with an episodic course. The main symptoms include a painful red eye, photophobia, and visual impairment. The prognosis is mostly good because patients present to the ophthalmologist and treatment is given at an early stage.

Uveitis screening: The table summarizes the currently recommended intervals for uveitis screening that are adapted to the uveitis risk of the individual JIA categories. The screening aims to detect uveitis before irreversible sequelae can develop. Routine examinations with medical history, visual acuity, slit lamp, tonometry, and funduscopy can be undertaken in any ophthalmological practice. Where complications are clinically suspected, additional investigations are required that are based on the findings.

JIA-Subgroup	ANA	Age at JIA onset (in years)	JIA duration (in years)	Recommended screening intervals (in months)
OA, RF-PA, PsA, AA	+	≤ 6	≤ 4	3
OA, RF-PA, PsA, AA	+	≤ 6	> 4	6
OA, RF-PA, PsA, AA	+	≤ 6	≥ 7	12
OA, RF-PA, PsA, AA	+	> 6	≤ 2	6
OA, RF-PA, PsA, AA	+	> 6	> 2	12
OA, RF-PA, PsA, AA	-	≤ 6	≤ 4	6
OA, RF-PA, PsA, AA	-	≤ 6	> 4	12
OA, RF-PA, PsA, AA	-	> 6	n.a.	12
ERA	n.a.	n.a.	n.a.	12
RF+ PA, Sys A	n.a.	n.a.	n.a.	12
Patients with uveitis	n.a.	n.a.	n.a.	According to uveitis course

Sys A = systemic arthritis; OA = oligoarthritis; RF-PA = seronegative polyarthritis; RF+PA = seropositive polyarthritis; ERA = enthesitis-related arthritis; PsA = psoriatic arthritis; AA = other arthritis. n.a. = not applicable

Anti-inflammatory therapy: Therapy of JIA associated uveitis is guided by the severity of inflammation and complications. Topical corticosteroids are generally used as the initial treatment. Severe uveitis is commonly treated with immunosuppressive drugs. Methotrexate is presently the first-choice agent. If uveitis is not responding, another immunosuppressive agent or biological is applied. Currently, adalimumab is the preferred TNF-inhibitor. In refractory disease, other biologicals are used (e.g., abatacept, tocilizumab or rituximab). Ocular corticosteroid injections / - implantations are considered as "rescue therapy". Controlled studies are warranted to offer most effective and safe therapy for children with JIA associated uveitis. Better knowledge of the basic mechanisms underlying the disease and of the molecules that are important for regulating inflammation may help to create new and more specific treatment approaches.

Management of complications: Cataract surgery is technically demanding because of the accompanying risk of subsequent harms in the anterior ocular segment (for example, synechiae, opacities of the vitreous). Using a "small incision technique" and ensuring complete perioperative inflammation control in specialist centers can nowadays justify implantation of intraocular lenses in selected patients from school age.

Glaucoma is often not adequately controlled with the available pressure-lowering medications, hence surgery is required. The currently favoured method entails filtrating interventions with intraoperative topical application of antimetabolites and drainage implants.

Macular edema in uveitis requires systematic treatment. The ocular inflammation should be treated according to current standards. In case of therapeutic failure when using acetazolamide, parabulbar and/or systemic corticosteroids, intravitreal corticosteroids or anti- VEGFs should be administered where necessary.

Recommended literature on the topic

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Kotaniemi K, Kautiainen H, Karma A, Aho K. Occurrence of uveitis in recently diagnosed juvenile chronic arthritis. A prospective study. Ophthalmology 2001;108:2071-5.

Sijssens KM, Rothova A, Berendschot TTJM, de Boer JH. Ocular hypertension and secondary glaucoma in children with uveitis. Ophthalmology 2006;113:853-9.

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NOTES

MCQ's

All of the following diseases may be associated with an herpes virus infection except

- ❑ Fuchs uveitis
- ❑ Posner-Schlossman syndrome
- ❑ Herpes zoster ophthalmicus
- ❑ Kaposi sarcoma
- ❑ EBV-associated uveitis

All of the following are classical manifestations of herpetic viral uveitis except

- ❑ High IOP
- ❑ Sectoral iris atrophy
- ❑ Granulomatous KPs
- ❑ Extensive posterior synechiae
- ❑ Mild AC flare and cells

Treatment of acute HSV-1 associated anterior uveitis does not include

- ❑ Valacyclovir 3g/d
- ❑ Topical corticosteroids
- ❑ Topical acyclovir ointment
- ❑ Beta blockers
- ❑ Dorzolamide

Herpetic Ocular Disease

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The author acknowledges no financial interest in the subject matter of this presentation

Viral infections

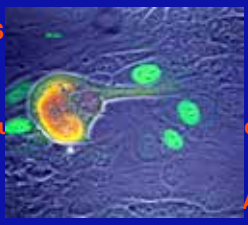
- **Viruses : one of the most exciting groups of pathogens**
- **Highly adapted opportunistic agents**
- **Evolving in symbiotic relation with their hosts**
- **Major improvement after specific therapy makes prompt diagnosis essential**
- **Two different groups : classical and emerging viral diseases**

Herpes viruses

- HSV1,2 (6.4% of uveitis and 25% of anterior uveitis)
- VZV (HZO, HZSH, Chickenpox)
- CMV (retinitis and CAU)
- EBV (retinitis and CAU)
- HHV-6,7 (retinitis)
- HHV-8 (conjunctivitis and panuveitis)
- HHV-???

Revolution in the field of uveitis

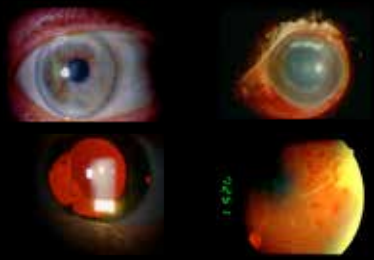
Posner-S



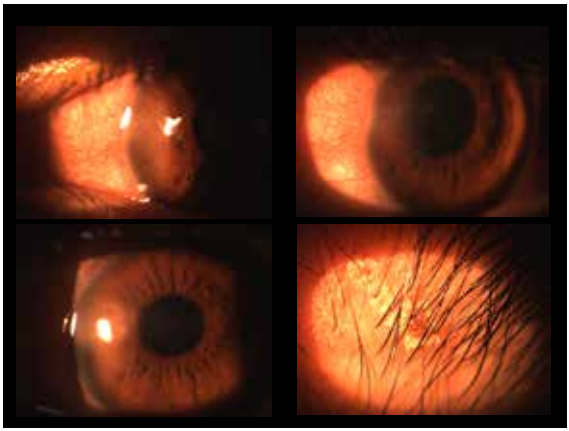
Fu clitis

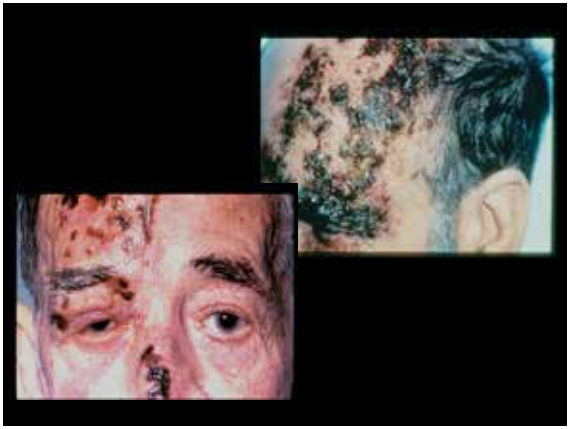
IOHS A

Pathophysiology



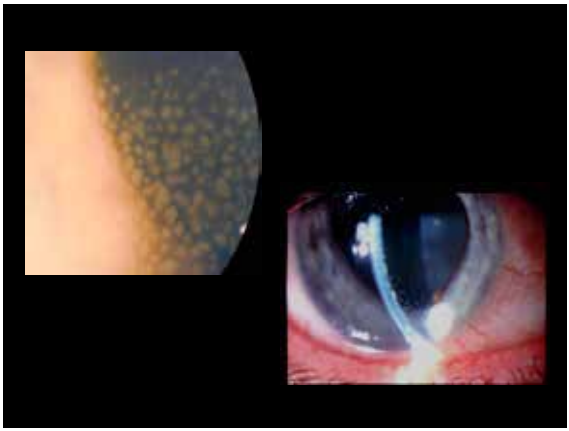
Love-hate relationship between herpesviruses and their cellular host

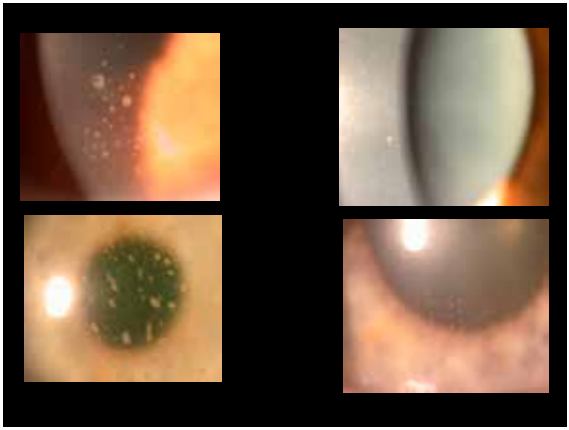


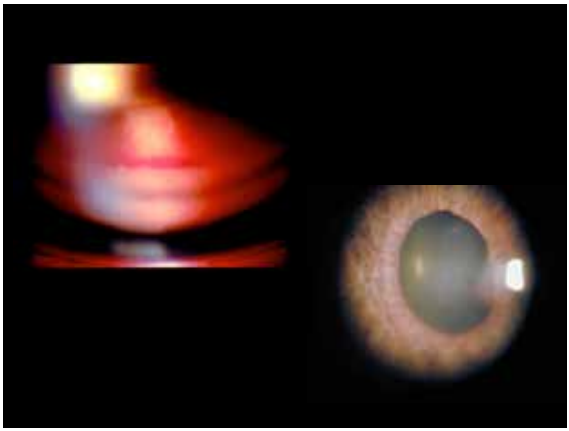


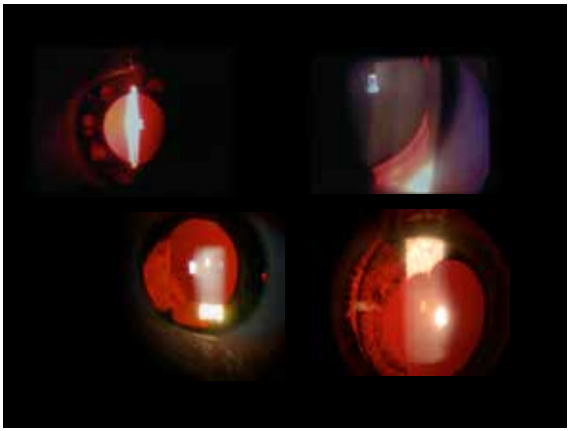
Rx of HZO without AU

- Within the first 72 hrs
- ValACV in IC patients
- 1g x3/d
- Duration of 8 days
- Decreases the risk of ocular complications (50%)









Diagnostic confirmation

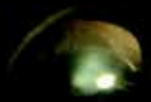
Direct evidence
- Culture

Indirect evidence
CBCC
Serology, GWC
PCR technology

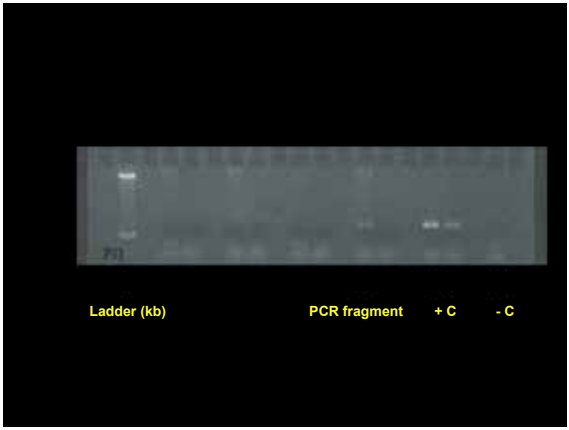
Specimens
- Blood
- Lymph nodes
Peripheral biopsies

- AH
- Vitreous
- Retina

Ocular fluid analysis



Polymerase Chain Reaction and Goldmann-Witmer Coefficient Analysis Are Complimentary for the Diagnosis of Infectious Uveitis



PCR

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

Lightcycler

ABI PRISM 7000

Dworkin et al. Arch Ophthalmol, 2002

Therapeutic management

Presumed herpetic uveitis

Diagnostic confirmation if necessary

Anti-inflammatory Rx
Topical steroids+++
Always associated with antivirals
Progressive tapering
Find the minimal dosage

Antiviral Rx
ValACV
Iv ACV?
Progressive tapering

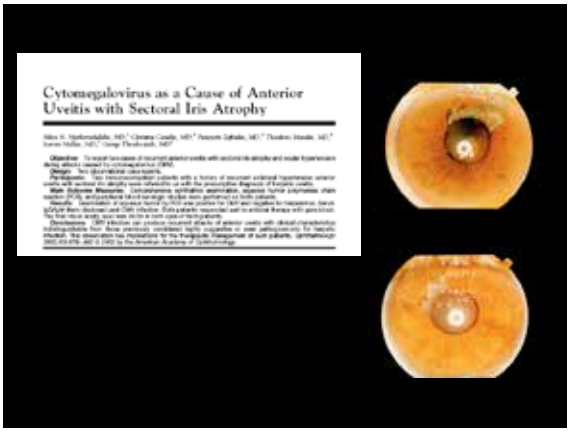
Anti-glaucomatous Rx

Duration?

Challenge

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

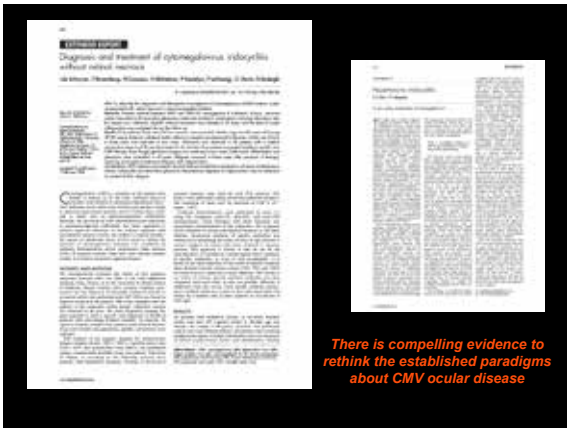
Wensing et al. Ophthalmology, 2011



Possible role of CMV infection in the etiology of the PS syndrome

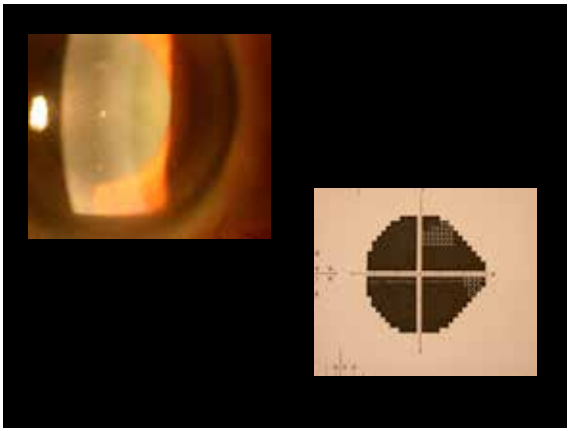
First report
Before PCR era
GW+
Not confirmed by another group
Remained controversial
No Rx at that time

Bloch-Michel et al. Int Ophthalmol, 1987

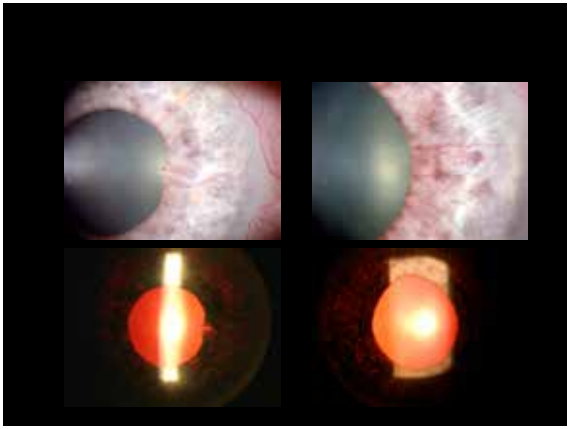


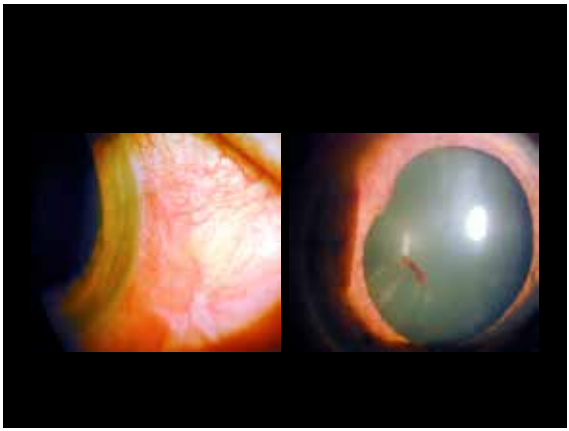
Diagnosis and treatment of cytomegalovirus vitreoretinitis without retinal necrosis

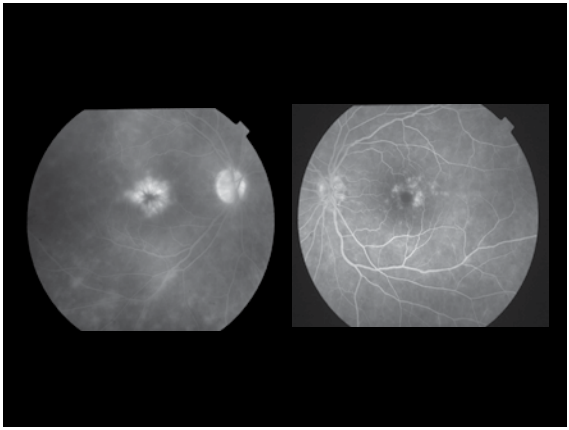
There is compelling evidence to rethink the established paradigms about CMV ocular disease

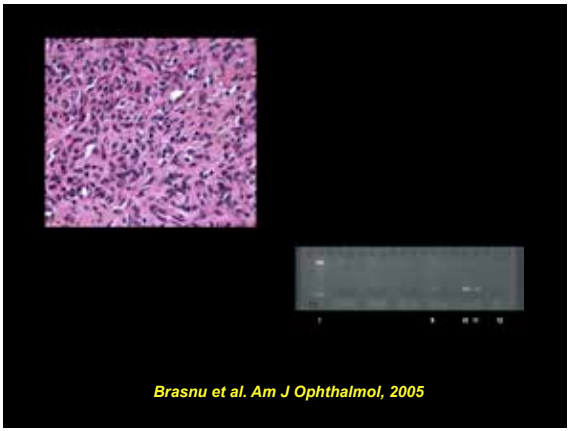


- 103 eyes
- Suspicion of PSS or FHC
- Singapore National Eye Centre
- 67 ACT in the PSS group : CMV+ in 52.2%
- 36 ACT in the FHI group : CMV+ in 41.7%
- Older age at diagnosis, male gender, and nodular endothelial lesions significantly associated with CMV infection in presumed FHI eyes









Summary

- Spectrum of infectious uveitis (especially herpetic diseases) has been revisited during the last decade
- Specific treatment improves the final prognosis of these cases
- New serologic and molecular procedures will allow us to better characterize clinical features associated with different genospecies

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Other viruses and anterior uveitis

Nikos Markomichelakis, Greece

08

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.

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

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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NOTES

MCQ's

Regarding ocular Toxoplasmosis:

- ❑ It is more frequently the result of congenital transmission
- ❑ Use of local depo steroids is a good alternative to treat active lesions
- ❑ Systemic steroids should only be used alongside anti-toxoplasmic drugs
- ❑ High intraocular pressure is not a feature of active retinitis

Toxocara ocular infections:

- ❑ May result in vision loss by directly affecting the posterior pole
- ❑ Is a very common occurrence in association with Visceral Larva Migrans
- ❑ Specific antibiotics are the treatment of choice
- ❑ The use of steroids in contra indicated

Diffuse Unilateral Sub-acute Neuroretinitis (DUSN)

- ❑ The presence of subretinal tracks is a common finding
- ❑ Yellow lesions disappear and leave pigmentary changes
- ❑ Loss of visual field is uncommon
- ❑ It is usually associated with multiple subretinal larvae

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, continental Europe or in North America. 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 infestations 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, but use of Azithromycin has been gaining popularity in view of the efficacy and safety profiles. Other options include Clindamycin, Spiramycin, Tetracyclines, 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.

Another option that has recently been explored is the use of intravitreal injections of Clindamycin associated with Dexamethasone, which has shown to be as effective

as systemic therapy and a goof alternative in cases of intolerance or significant side effects to systemic therapy.

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.

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.

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. The use of systemic antihelmintic drugs 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.

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 bovine for the first and the swine 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 semms 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.

OPHTHALMOMYIASIS

Ophthalmomyiasis is induced by the invasion of ocular tissue by fly larvae (maggots). It is classified regarding its location into Ophthalmomyiasis externa, characterized by the involvement of orbital or extraocular tissue, and Ophthalmomyiasis interna, when larval invasion of the globe is seen.

In the extraocular form, the deposition of a first stage larva into the orbit may cause conjunctival hyperaemia, chemosis, clear or purulent exudation, photophobia, epiphora, blepharospasm and palpebral edema. Foreign body sensation, itching and pain are the symptoms of extraocular infestation. The intraocular form is generally unilateral with the maggot penetrating the eye through the optic nerve, scleral emissary channels, via the blood stream or via surgical wounds.

The involvement of the posterior segment of the globe may occur in the form of vitreous invasion, leading to the perception of a floater or invasion of the retina by the maggot resulting in characteristic subretinal tracks with retinal pigment epithelial

disruption. Tracks may be accompanied by subretinal and vitreous hemorrhage. Inflammatory reactions due to the presence of the maggot vary from mild uveitis and vitritis to severe panuveitis.

Treatment aims at destroying the maggot, stopping the damage caused by its movement.

Argon laser-photocoagulation of the subretinal larva results in destruction of the larva by thermal denaturation without producing severe inflammation or allergic reaction.

Visual prognosis depends on involvement of the central macula by the moving parasite.

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NOTES

MCQ's

Which statement is true concerning ocular syphilis:

- ❑ Ocular syphilis is a frequent manifestation of primary syphilis
- ❑ Ocular involvement in secondary syphilis often follows months after the systemic manifestations (e.g. skin rash)
- ❑ Ocular involvement is more aggressive in tertiary than in secondary syphilis
- ❑ Anterior syphilitic uveitis responds well to topical steroids

Which statement concerning the diagnosis of ocular syphilis is true?

- ❑ Although syphilitic ocular involvement tends to be more aggressive in HIV+ patients, the serologic tests for syphilis are as reliable in HIV-positive as in HIV-negative patients
- ❑ PCR on aqueous is the gold standard for the diagnosis of ocular syphilis
- ❑ The major advantage of specific anti-treponema tests over the non-specific tests, is the fact that the decline in the titer of specific tests serves as a marker for the efficacy of the treatment
- ❑ The presence of specific anti-treponemal antibodies in cerebrospinal fluid is no proof of neurosyphilis

Advantages of the IGRA test in the diagnosis of TB includes the following:

- ❑ Easy to perform
- ❑ Cheap
- ❑ No cross-reaction with antigens from BCG vaccine
- ❑ Allows differentiation between active and latent TB

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 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 periphlebitis with 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 of 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 lympadenopathy.

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)

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

Resolution of inflammation and absence of recurrences = confirmation of "presumed" ocular TB

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.

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. Re-awakening 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, 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.

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.

Conclusion

Both syphilis and HIV infection are much more prevalent in the developing world. Ocular syphilis, probably more frequent in patients with HIV co-infection, causes a wide variety of ocular inflammatory conditions and 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.

Philippe Kestelyn
Ghent, Belgium

Viral retinitis
Bahram Bodaghi, France

11

MCQ's

Viral retinitis

- ❑ Is the most frequent etiology of posterior uveitis
- ❑ Is an absolute emergency
- ❑ Is associated with HSV-2 in the elderly
- ❑ Occurs exclusively in immunocompromised patients
- ❑ Is usually bilateral

Clinical manifestations of ARN syndrome does not include

- ❑ Peripheral foci of retinitis
- ❑ Granulomatous anterior uveitis
- ❑ Dense vitritis
- ❑ Relapses in the same eye
- ❑ Retinal vasculitis

CMV retinitis

- ❑ Is a major cause of blindness in patients with early HIV infection
- ❑ Occurs if the rate of CD4 is above 300/ mm^3
- ❑ Is a rapidly progressing disease
- ❑ Is associated with a dense vitritis
- ❑ Must be treated with oral valgancyclovir

The widening spectrum of viral retinopathies

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The author acknowledges no financial interest in the subject matter of this presentation

Introduction

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

Kirisawa's uveitis

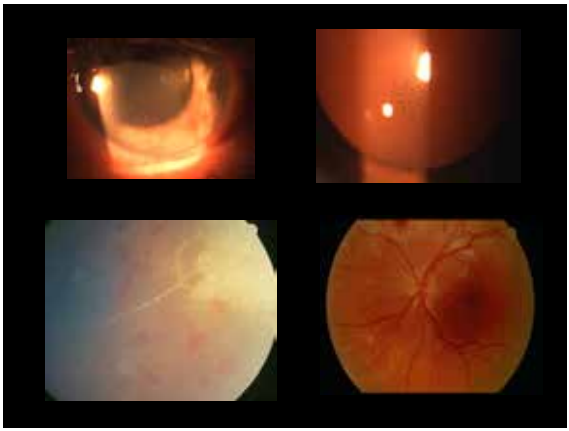
(*Urayama et al.* 1971)

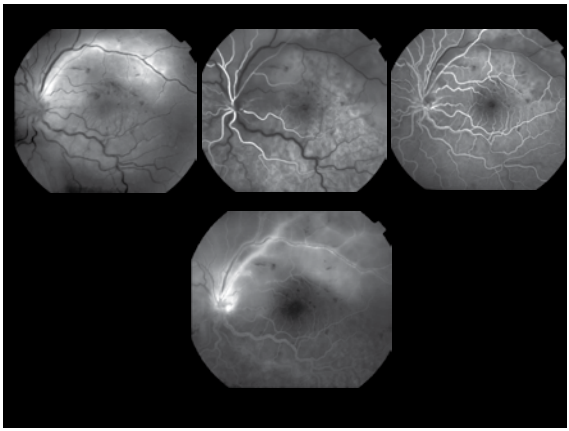
- Acute uveitis
- Retinal obliterative vasculitis
- Confluent yellow-white lesions
- Retinal periphery

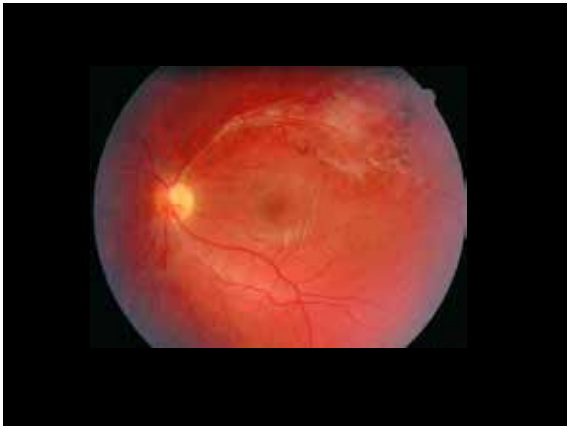
ARN syndrome

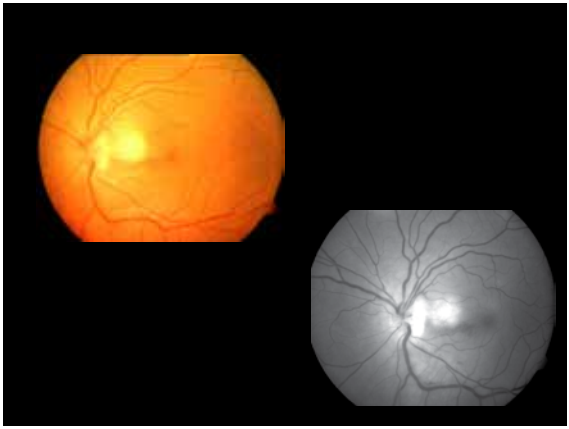
- Focal, peripheral well-demarcated areas of retinal necrosis
- Rapid and circumferential progression
- Vitritis+++ and AAU
- Occlusive vasculopathy
- IC or IS patients

- ~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

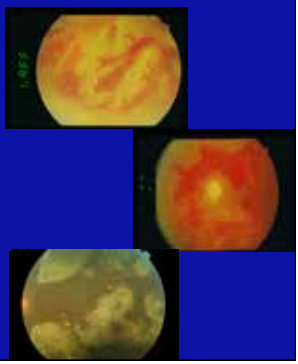
PCR analysis from AH

- 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+++



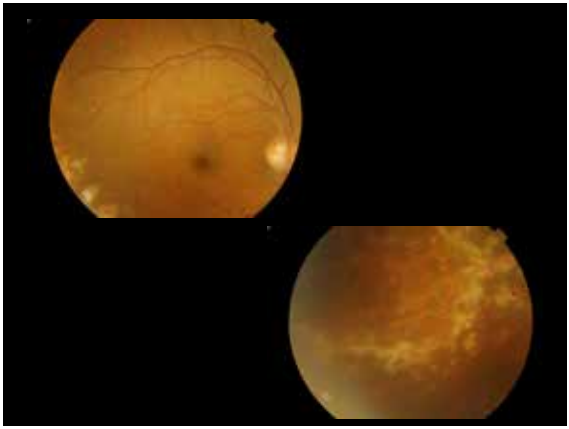
HAART era

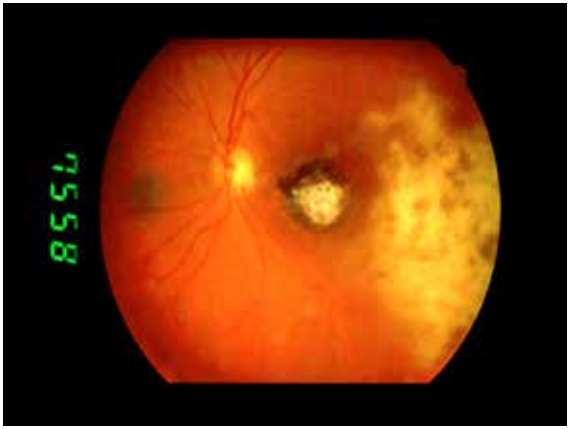
- Incidence of CMV retinitis : 5.6/100 PY (most in HAART-failure patients)
- IRU : response to CMV antigens
- Incidence 0.1-0.8 PY of follow-up
- Similar pattern in patients with previous ocular toxoplasmosis and TB

Holland, Am J Ophthalmol, 2008

Jabs, Arch Ophthalmol, 2008

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

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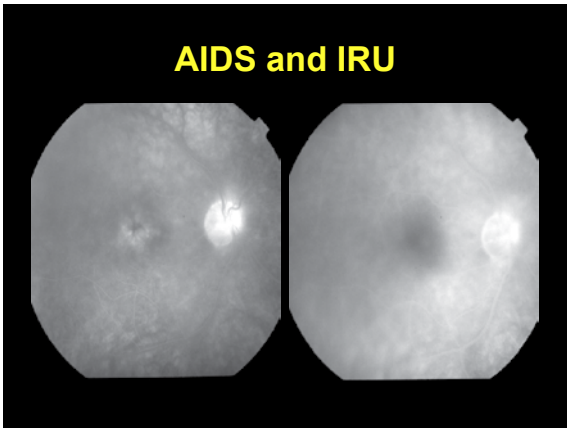
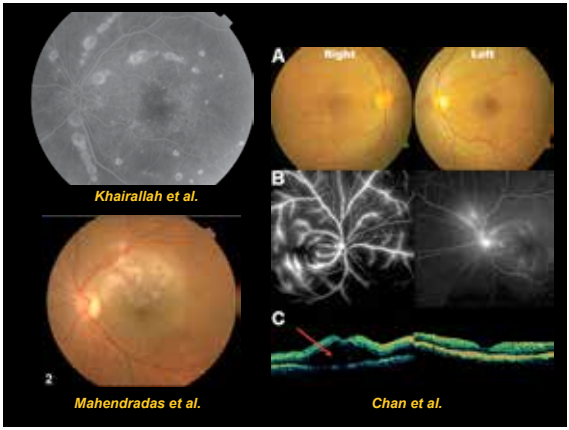
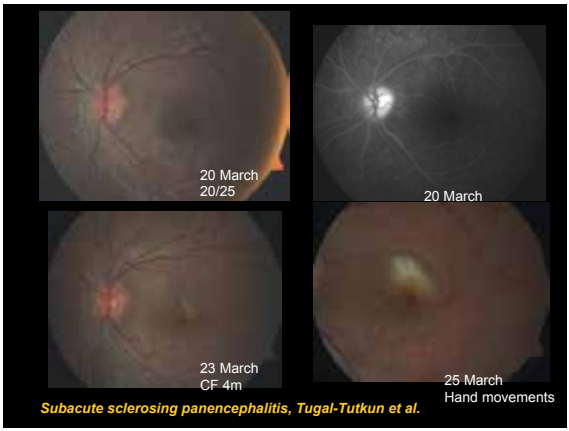
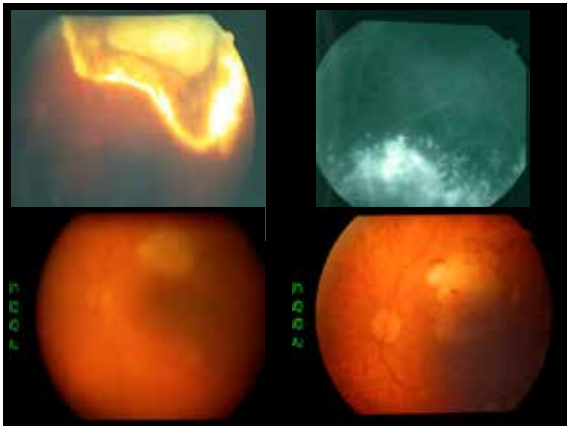

AIDS and IRU


Khairallah et al.
A
Right
Left
B
C
2
Mahendradas et al.
Chan et al.



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

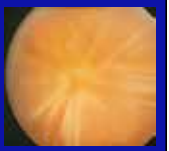
- followed by oral valacyclovir **: 1g x 3/day**
(val ACV) for 6 weeks

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

- 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

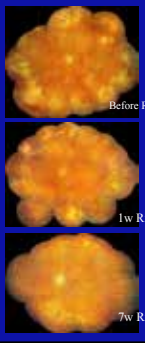
Meghpara B et al. 2010

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



Double-blind study comparing 2 dosages of valacyclovir hydrochloride for the treatment of uncomplicated herpes zoster in immunocompromised patients 18 years of age and older.

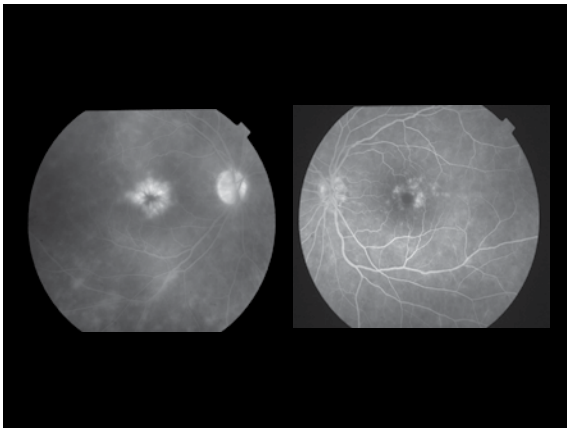
- 1g TID vs 2g TID
- Herpes zoster in IS patients
- 2g TID reaches ACV plasma levels similar to those achieved with iv ACV (10 mg/kg every 8 h for 7 days)

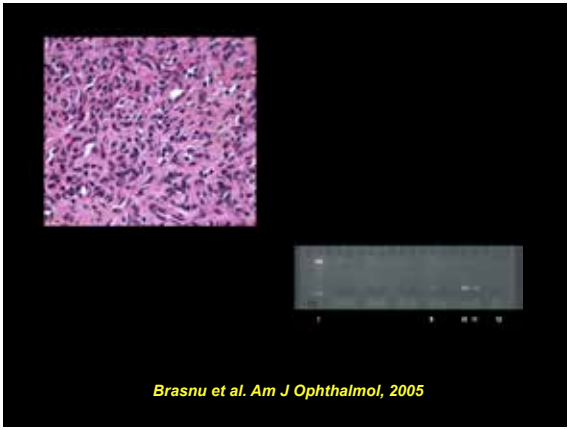
Arora et al. J Inf Dis, 2008

Emerging entities

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


Necrotizing Herpetic Retinopathies Masquerading as Severe Posterior Uveitis

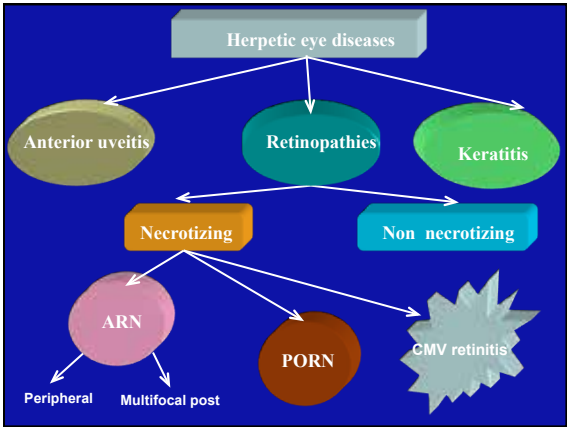



Brasnu et al. Am J Ophthalmol, 2005

Necrotizing and nonnecrotizing variants of herpetic uveitis with posterior segment involvement.

Description of a group of patients with different forms of viral retinopathies

Wensing et al. Arch Ophthalmol, 2011



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

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MCQ's

What signs and symptoms would make you suspect endophthalmitis?

- ❑ Worsening of visual acuity with no evident pathology in the microscope 4 wks after cataract surgery
- ❑ Drop of visual acuity to LP, hypopyon and poor view to retina 4 days after cataract surgery.
- ❑ Sudden drop of visual acuity, no anterior chamber reaction, loss of red reflex in a diabetic.
- ❑ Sudden loss of vision after blunt trauma in a patient operated for cataract 15 years ago. Clear media.

What is your first measure when you suspect an endophthalmitis in a patient seeing LP only after previous surgery?

- ❑ Schedule the patient for intraocular culture sampling with injection of intravitreal antibiotics as soon as possible.
- ❑ Schedule the patient for vitrectomy with intraocular culture sampling and injection of intravitreal antibiotics as soon as possible
- ❑ Take a conjunctival smear
- ❑ Send the patient to a CT scan.

What organisms cause the most devestating course of endophthalmitis?

- ❑ Coagulase negative staphylococci
- ❑ Candida
- ❑ Streptococci
- ❑ P. acnes

Endophthalmitis, i.e. infection in the anterior chamber and/or the vitreous, is a rare but much feared ocular emergency. The majority of cases are seen following intraocular surgery.[1] Other causes are perforating trauma or septicemia. Distinguishing frank intraocular infection from sterile inflammation may at times be challenging and one should always a high index of suspicion when confronted with inflammation out of proportion with a preceding surgical trauma or as in the case of a possible endogenous endophthalmitis, a recognized risk factor such as immunosuppression or intravenous drug abuse.

The intraocular environment is sterile. Invading bacteria or fungi multiply and the generation of toxic products and/or the action by the mounted host inflammatory response may in the worst case scenario lead to retinal damage. The process may at best be halted or modified by prompt treatment.

Epidemiology

The greatest numbers of endophthalmitis incidents appear after cataract surgery and intravitreal injections (IVT), simply because these are the most commonly performed intraocular operations nowadays.[1-3] The highest incidence, however, is seen after perforating trauma (1 – 5%).[1] In contrast, the rate after cataract extraction and IVT may be as low as 0.02% – 0.05%.[2,3] Other procedures like trabeculectomies, corneal transplants and vitrectomies seem to carry a somewhat higher risk.[4] Prophylactic antibiotics and disinfectants are widely used to prevent infection, but there is no universally accepted prophylactic regime apart from taking measures to preserve sterility. The highest level of evidence has been found for the use of intracameral antibiotics in cataract surgery.[5]

Examination and diagnosis

Typically, the patient experiences a sudden or rather fast worsening of vision. Usually it deteriorates to finger counting. Redness of the eye is common. Pain can be severe but is not always present. In the microscope, the examiner will see anterior chamber flare and most often a hypopyon. Vitreous clouding compromising visualization of retinal structures is another hallmark sign. Fungal endophthalmitis may have a more insidious course with a moderate effect on the red reflex. In such cases retinal infiltrates are usually discernable.

Intraocular culture sampling is mandatory and is easily performed as a tap of the anterior chamber (50% sensitivity) and of the vitreous (70% sensitivity). Positive results are increased if a diagnostic vitrectomy is performed and if a supplementary PCR analysis is undertaken. In septicemia, blood cultures are valuable.

Etiology of endophthalmitis

In cases of postoperative endophthalmitis, the organisms originate from the patient's conjunctiva. Gram-positive bacteria like coagulase-negative staphylococci dominate whereas gram-negatives make up roughly 10% of positive cultures. In post-traumatic cases, contamination occurs via the perforating body and gram-negatives and fungi are more common. With endogenous endophthalmitis, a focus of infection is known or has to be looked for.

Treatment

Antibiotics should be injected directly into the vitreous at the same time as the diagnostic sampling is performed. In the Western World, vancomycin together with an agent covering gram-negatives is the back-bone regime. The risk for fungal infections should be considered after trauma or in endogenous endophthalmist (or in all cases in tropic climates) and e.g.amphotericin B should be added. There is no proof that systemic antibiotics have an add-on effect to the intraviteral protocol, but they are mandatory in septicaemia. If presenting vision is worse than the perception of hand movements, a therapeutic vitrectomy should be carried out with no delay according to a large multicentre prospective study. Systemic steroid treatment is considered beneficial, whereas there is no consensus regarding intravitreal administration.

Outcome

The kind of causative organism is the strongest determinant for the outcome among post-operative cases. Culture-negative cases and those infected with coagulase-negative staphylococci do quite well and may even experience full visual recovery. Streptococcal infection carries a poor prognosis as do post-traumatic and endogenous endophthalmitis incidents in general.[7]

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3. Nentwich M, Yactayo-Miranda Y, Schwarxbach F, Wolf A, Kampik A, Mino de Kaspar H. Endophthalmitis after intravitreal iunjection. Retina 2014; 34: 943 – 50.

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7. Ness T, Pelz K, Hansen LL. Endogenous endophthalmitis: microorganisms, disposition and prognosis. Acta Ophthalmol Scand. 2007; 85: 852–856.

Endophthalmitis
Per Montan, MD, Ph D
St Erik Eye Hospital, Stockholm, Sweden

MCQ's

What signs and symptoms would make you suspect endophthalmitis?
Primary Intra-Ocular Lymphoma is:

- ❑ a Hodgkin's lymphoma in most of the cases.
- ❑ always preceded by Central Nervous System lymphoma
- ❑ lethal
- ❑ most of the time observed in patients under 60 years of age

Among the following signs of Primary Vitreo-Retinal Lymphoma, which one is the less frequent:

- ❑ floaters perception
- ❑ iris posterior synechiae
- ❑ non painful eye
- ❑ leopard appearance on fluorescein angiograms

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 (Primary Vitreo-Retinal Lymphoma previously named Primary Intra-Ocular 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)

Uveitis-like syndrome and iris transillumination after the use of oral moxifloxacin

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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NOTES

Intermediate/pars planitis

Talin Barisani Asenbauer, Austria

14

Intermediate uveitis (IU) was first described as chronic cyclitis by Ernst Fuchs in 1908. In the Standardization of Uveitis Nomenclature (SUN) working group's international workshop for reporting clinical data the consensus was reached that the term IU should be used for that subset of uveitis where the vitreous is the major site of the inflammation and encompasses the entities pars planitis, posterior cyclitis, and hyalitis.

The presence of i.e. peripheral vascular sheathing, macular oedema, optic disc oedema or anterior chamber cells should not change the classification.

Anatomic Classification	Primary Site of Inflammation	Includes
Anterior Uveitis	Anterior chamber	Iritis, Iridocyclitis, Anterior cyclitis
Intermediate Uveitis	Vitreous	Pars Planitis, Posterior Cyclitis, Hyalitis, Vitritis
Posterior Uveitis	Retina and/or choroid	Focal, multifocal, diffuse, or geographic Choroiditis Chorioretinitis Retinochoroiditis Retinitis Neuroretinitis
Panuveitis	Anterior chamber, Vitreous, and Retina or Choroid	

Tab 1: SUN classification (Jabs et al, AJO 2005)

Pars planitis is considered a subset of intermediate uveitis and is characterized by the presence of snowbanks (white exsudates) over the pars plana/ora serrata or snowballs (aggregation of inflammatory cells) in the vitreous in the absence of an infectious etiology or a systemic disease.

Epidemiology

Incidence of all uveitis cases in Europe and USA are estimated between 17-50/100.000
Around 20% IU
In adults 60% idiopathic up to 40% associated systemic diseases

- Multiple sclerosis
- Sarcoidosis
- Infectious (TbC, Syphilis, Borreliosis, HTLV ..)
- Masquerades (Lymphoma, Leucemia, Amyloidosis, Neoplasms)
- Whipples Disease

In children around 20% of cases are associated with systemic diseases (i.e. JIA, TINU syndrome, post-streptococcal syndrome)

Familial cases of pars planitis have been reported, suggesting a possible genetic predilection or a common environmental factor that may predispose certain individuals to develop pars planitis.

Human leukocyte antigen (HLA) DR15 has been associated with pars planitis. HLA-DR15 is also associated with MS, optic neuritis, and narcolepsy.

SIGNS and SYMPTOMS

Patients with intermediate uveitis typically report blurred vision and floaters.
Only when the anterior chamber is involved pain and photophobia are reported (rare)
The conjunctiva is typically white and uninflamed.
The vitreous is the site where the inflammation is concentrated: varying amount of cells, fibrin, and cellular debris.

In pars planitis inflammatory exudates, snowballs and snowbanks, may form in the inferior vitreous base, over the peripheral retina, and the pars plana.

Retinal periphlebitis (i.e., sheathing), optic disc edema, and macular edema are present in some cases.

CLINICAL COURSE

The clinical course is marked by chronic low-grade inflammation with episodes of exacerbation. Often bilateral cases, in unilateral cases consider HCF.

COMPLICATIONS

Cystoid macular edema (up to 50%)
Cataracts (5% to 42%)
Periphlebitis (16-36%.)
Epiretinal membranes (~30%)
Retinal detachment
Vitreus hemorrhage
Optic disc swelling
Neovascularization
Retinoschisis
Cyclitic membrane

Cystoid macular oedema and snowbanking have been reported to be associated with a worse visual outcome.

DIAGNOSIS

The diagnosis of IU is based completely on history and clinical findings.

The patient's history should concentrate on the duration of symptoms, the number of recurrences, and findings that might be associated with systemic disorders.

Work-Up

1. *Medical History*

Ocular symptoms. (floaters, metamorphopsies, visual acuity changes?),
Duration? Acute or chronic? Persistend or recurrent?
History of previous ocular inflammation?
History of ocular surgeries/trauma?
Known Systemic diseases?

Systemic symptoms? Fever, fatigue, or night sweats (i.e. sarcoidosis/tuberculosis), whereas loss of sensitivity or paresthesias (MS?). Dermatitis (Borreliosis/tuberculosis/syphilis?), arthritis (Borreliosis?), domestic animals, cats (Bartonella?)

2. *Ophthalmic Examinations:*

- Visual acuity
- Biomicroscopy of anterior segment
- Tonometry
- Binocular examination of vitreous and posterior segment in mydriasis
- Classification of vitreous haze according to
- Optical coherence tomography (OCT) rule out cystoid macular edema
- Additional examinations:
- Perimetry in cases with optic disc involvement
- Echography in cases with reduced , rule out intraocular tumors
- Fluorescence angiography/ indiocyanine angiography in cases with suspected retinal/choroidal vasculitis, retinal non-perfusion, neovascularization and/or unclear findings
- Elektrophysiology (ERG, VEP, multifokales ERG): rule out neuritis and/or subclinical retinitis/ retinopathy
- Ultrasound biomicroscopy (UBM): visualization of pars plana exudates, rule out intraocular tumors.
- Diagnostic vitrectomy is done in cases when tumors are suspected, in patients with severe vitreous inflammation where retinitis, endophthalmitis cannot definitely be excluded and in cases where response to medical therapy is refractory.

3. *Baseline systemic workup*

comprising complete blood count which includes total and differential count/ hemoglobin/ platelet count, erythrocyte sedimentation rate, purified protein derivative skin test (PPD) and chest X-ray are mandatory.

A PPD test/Quantiferon test is needed to exclude tuberculosis.

In cases of IU, only a few laboratory and serologic tests are necessary. These tests include determination of the angiotensin-converting enzyme (ACE) level. Serologic testing for cat-scratch disease, syphilis, and Lyme's: disease should be seriously considered in cases of IU.

Taylored exclusion of systemic diseases as indicated by medical history

Nevertheless before initiating immunosuppressive therapies infections as tuberculosis and diseases as multiple sclerosis have to be excluded.

Imaging: Chest Xray/CT scan (sarcoidosis/tuberculosis)
Cerebral MRI with contrast (multiple sclerosis)

HCF: Rubella Antibody PCR from anterior chamber tap

4. *Differential diagnoses*

Lyme's disease (*Borrelia burgdorferi*),
toxoplasmosis,
toxocariasis,
tuberculosis,
syphilis,
multiple sclerosis,
sarcoidosis
intraocular lymphoma
Behcet´s Disease
Immune recovery uveitis
Whipple Disease
human lymphotropic virus Type 1 (HTLV-1),
Epstein-Barr virus
cat-scratch disease (*Bartonella henselae, B quintana*)
Chronic propioniobacterial endophthalmitis

Primary ocular lymphoma should be ruled out in patients older than 50 years with persistent unresponsive intermediate uveitis.
Drug induced uveitis should be considered in patients with uveitis beginning days to months after initiating of new therapies
In children: renal diseases (tubulointerstitial nephritis and uveitis syndrome (TINU syndrome), and mesangial glomerulonephritis), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, post-streptococcal uveitis.

Important diagnostic features to be considered/ruled out before initiating systemic therapies:

- Heterochromic cyclitis Fuchs (HCF): upto 80% of cases show vitreous involvement. Rubella PCR from anterior chamber tap.
- Multiple sclerosis: rule out before initiating TNF-alpha inhibitors!
- Infectious uveitis: tuberculosis, Lyme disease
- Consider masquerade if uveitis is therapy refractive

Treatment:

- a mild IU without reduction of the visual acuity and without ocular complications can be monitored without therapy

in section 5 treatment options will be presented

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Birdshot Retinochoroidopathy

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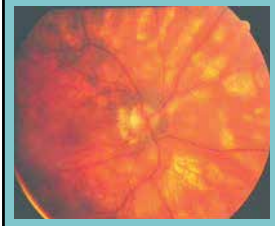
Clinical Diagnosis

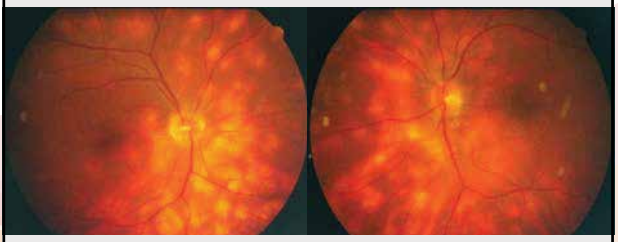
- **Well defined criteria**
  - White, painless eyes
  - Minimal anterior segment inflammation
  - Floaters, photophobia, disturbed color vision
  - Vitritis without snowballs or snowbanks
  - Elongated cream-colored or depigmented spots scattered throughout the post-equatorial fundus
  - Retinal vascular leakage leading to CME

Introduction

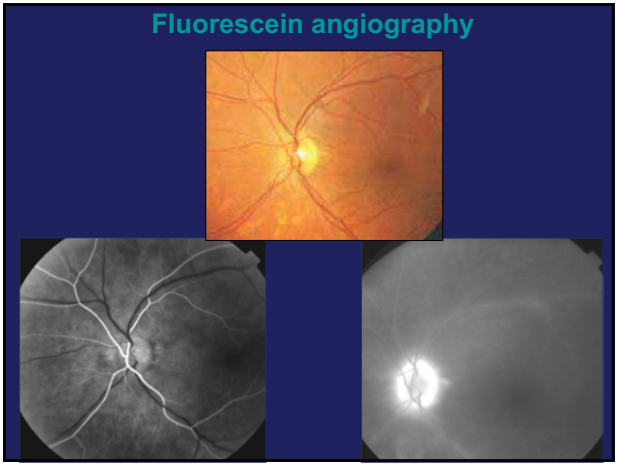


- Typical BRC lesions : scattered cream-colored spots

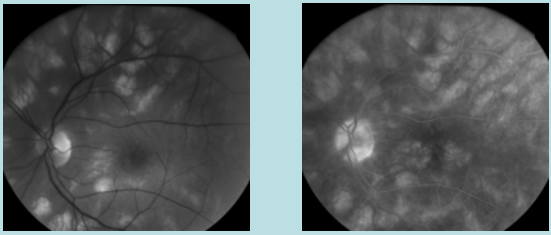
Fundus examination



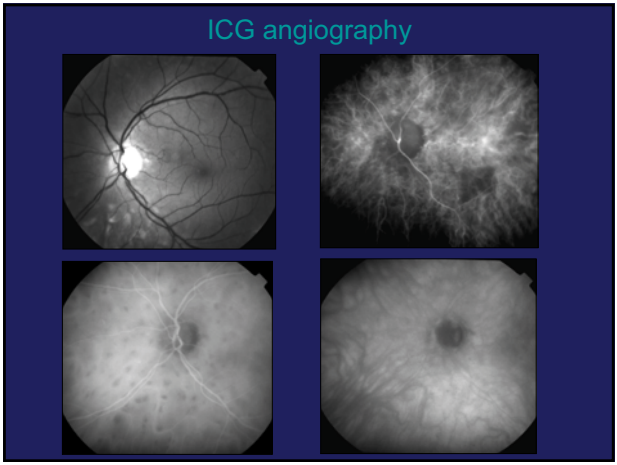
- **Deep pale round or oval spots**
  - **in the posterior pole and middle periphery**
  - **predominantly located in the nasal inferior peripapillary area**
  - **some of them are confluent next to the optic nerve edge**
  - **others radiate toward the periphery**

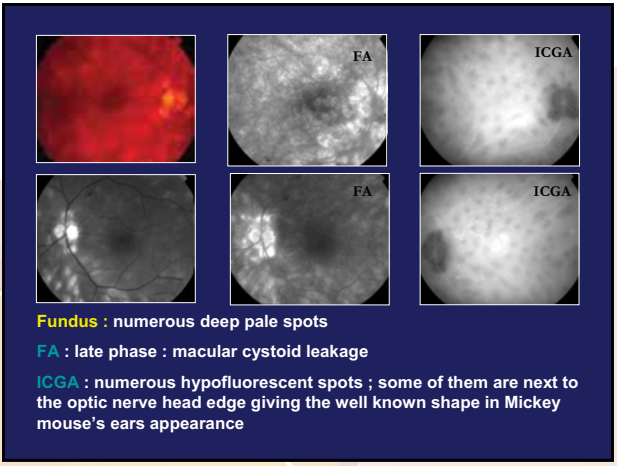


Fluorescein Angiography



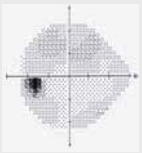
- Red free photograph : well defined spots
- FA : hyperfluorescence of the optic disc, spots, CME

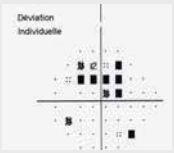

ICG angiography

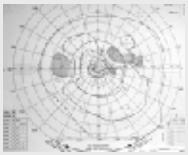

FA
ICGA
FA
ICGA
Fundus : numerous deep pale spots
FA : late phase : macular cystoid leakage
ICGA : numerous hypofluorescent spots ; some of them are next to the optic nerve head edge giving the well known shape in Mickey mouse's ears appearance

Visual field alterations

- **Enlarged blind spot**
- **Central or paracentral scotomas**
- **Diffuse decrease in global sensitivity**



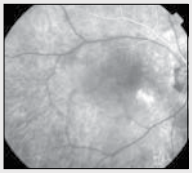


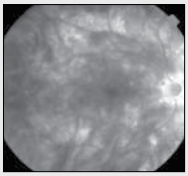


Humphrey 25.2 **10.2** **Goldmann**

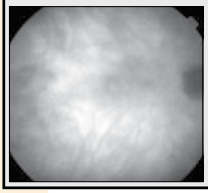
→de Courten C, Herbort CP, Arch Ophthalmol 1998

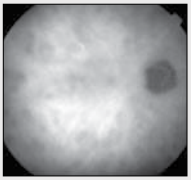
Visual field alterations

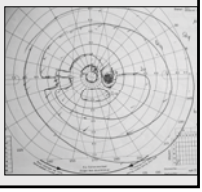




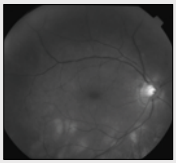
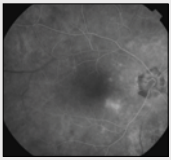
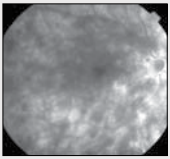
1998 BCVA 1.0



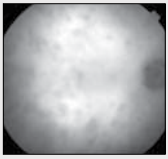
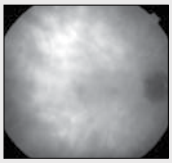
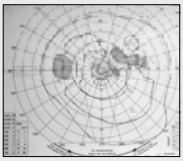




Visual field alterations

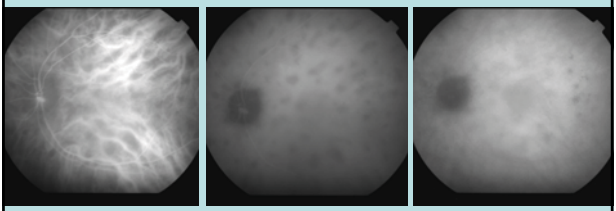
2003 BCVA 1.0

Clinical Diagnosis

- **Other important features**
  - Optic disc involvement +++
  - Causes of decreased vision : CME+++, ERM, CNV
  - Presence of the **HLA-A29 antigen (90-98%)**
  - ICG-A presentation
  - ERG alterations (30-Hz flicker implicit times)
- **Differential Diagnosis**
  - Sarcoidosis
  - tuberculosis
  - lymphoma

Indocyanine Green Angiography

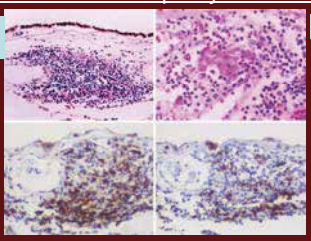


- Well delineated hypofluorecent choroidal spots

Birdshot Retinochoroidopathy: choroidal infiltrates

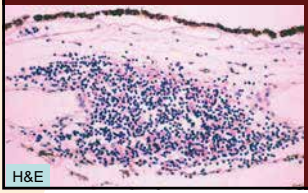
Non-granulomatous

Granulomatous



CD-8

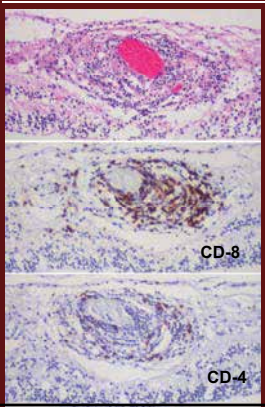
CD-68



H&E

1. Multifocal lymphocytes aggregates and occasional granulomatous infiltrates at perivascular sites in the mid choroid
3. Preservation of choriocapillaris
4. The lymphoid infiltrates are made up of mainly CD-8 positive cells
5. Similar lymphoid infiltration is seen around the retinal vessels.

Birdshot: Retinal vasculitis



Birdshot

The retinal vascular infiltration

Non-granulomatous
lymphoid infiltration
of the retinal vessels, mostly perivascular distribution

The infiltrate is made up of mainly CD-8 cells

Few CD-68 positive histiocytes and CD-4 positive T- cells are present

Major Issue = Treatment

- Should we treat ?
- How aggressively should we treat ?

Early 80'S till the mid 90's

- No need for Rx unless the vision deteriorates to less than 20/40
- Because : !!!!!
  - We don't know the natural course of the disease !!!
  - There were no "controlled trials" !!!!
  - The majority of the patients retain an acceptable vision !!!!
  - The side effects induced by the Rx (CT, IMT …)

Should we treat ?

- Until recently: indications for Rx limited to very severe cases with VA below 20/40
- Since 2000, several longitudinal studies show the poor visual prognosis of BRC
- The same authors who denied the need for any Rx in the past, are now favoring an aggressive Rx in the early active phase of the disease.

Why should we treat ?

- Severity of the disease
- Poor visual outcome
- Chronic macular oedema+++
- Progressive loss of VA during follow-up
- The number of eyes with VA less than 20/200 increased :
  - From 8% at onset
  - To 30% after 5 years
  - To 39% after ten years of follow-up

(Rothova *et al*. Ophthalmology, 2004)

- An aggressive therapeutic approach might be justified (CME+++)

(Thorne *et al*. Am J Ophthalmol, 2005)

Initial Treatmentssss ?!!?!

- No treatment : sometimes, very rarely
- Topical steroids = NO !!
- Peri-ocular steroids = ??
- Intraocular steroids = ?? *(intravitreal injections or corticosteroid device)*
- Systemic Rx +++
  - Corticosteroids :
    - oral prednisone 1 mg/kg/d
    - pulse i.v. methylprednisolone
  - Corticosteroid-sparing agents

Treatment of Birdshot retinochoroidopathy

- No intervention : simple observation + monitoring

- Systemic corticosteroids
- Corticosteroid sparing agents
  - *IVIg (intravenous polyclonal immunoglobulins)*
  - *cyclosporine ± azathioprine*
  - *MMF*
  - *IFN?*
  - *Daclizumab (Zenapax)*

Conventional TT : Steroid therapy

Initiated by pulses of methylprednisolone

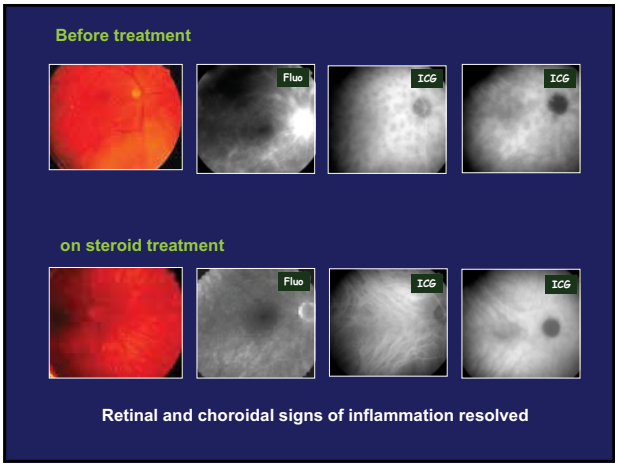
Followed by prednisone 1 mg/kg/d

General and Opthalmologic assessment at 3 weeks

So as to precisely determine how is the lesions steroid sensitivity

Tapering and follow up to determine the steroid daily threshold

BRC often shows a high steroid theshold (20- 40 mg/d)



Corticosteroid-Sparing Agents

(high dose corticosteroids dependence > 20 mg/d oral prednisone)

- IvIg: polyclonal Ig (expensive, unconvenient but effective in mild cases)

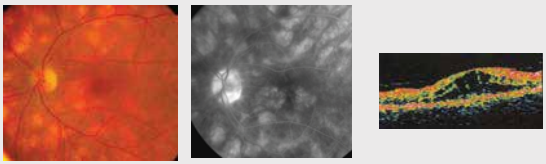
- Azathioprine
- Cyclosporine
- Mycophenolate Mofetil (MMF)
- Combination of Cyclosporine and MMF

Immunomodulation

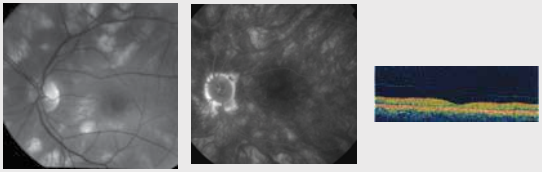
- **Polyclonal Immunoglobulins**
  - **from human origin (20 donnors)**
  - **induce saturation of idiotypic net**
- **Pilot study**
  Polyclonal immunoglobulins only
  18 patients VA ↑ 53% ↓18% with a mean follow up of 39 m
  Reduction of fluorescein leakage (50%)
- **Retrospective study**
  Combined therapy (Steroid + PIG) 37 patients
  Significant steroid threshold decrease

→P. LeHoang et al. Ocular Immunol Inflamm 2000

CME recurrence under Prednisone (15 mg/d)



Control of inflammation under prednisone 5 mg/d and polyclonal immunoglobulins 0.3g/kg/month



Cyclosporine = Not a New Rx

- 1983 = the first published BRC patient treated with Cyclosporine (*R.B. Nussenblatt*)
- 1988 = published positive results in a series of 19 BRC cyclosporine treated patients (*P. LeHoang*)
- 1994 = effectiveness of low-dose cyclosporine (*A.T. Vitale*)

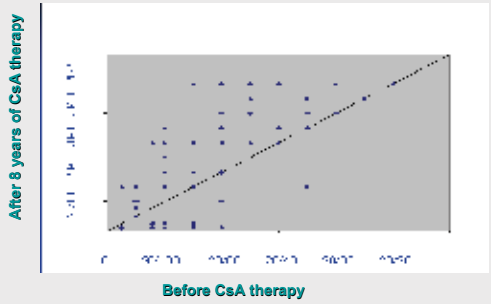
Patients and Methods

- Retrospective case study (severe forms of BRC)
- January 1986-january 2000
- Inclusion criteria :
  - Diagnosis based on : typical clinical presentation (Ryan and Maumenee, 1980)
  - HLA-A29+
  - Treated with CsA : dependence or resistance to high dose Ct, resistance to Ivlg
- Cyclosporine A :
  - Started at 3-5 mg/kg/d
  - Slowly tapered
- Efficacy of CsA was evaluated :
  - VA, severity of macular edema (FA +/- OCT)
- Safety of CsA was evaluated :
  - Renal function and blood pressure

Results 1

- 168 BRC managed (1986 - 2000)
- 49 patients (98 eyes) required CsA (29.16%)
- Average age at onset : 48.5 years (29-68 y)
- Caucasian (100%)
- F/M : 1.2
- Mean duration of disease before CsA : 4.5 y (1-14 y)
- 28 patients required high level of Ct (57.1%) > 25 mg/d
- Resistance to Ct : 21 patients (42.9%)
- Control of ocular inflammation was achieved in most of cases
- Major renal toxicity
  - observed in 2 patients
  - required a rapid dosage tapering of cyclosporine
  - Azathioprine was added

Visual acuity



- Improved by 2 lines or more : 42 eyes (42.6%)
- Stabilized : 37 eyes (38%)
- Decreased by 2 lines or more : 19 eyes (19.4%)

Results 2

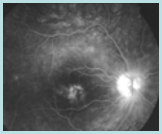
- CsA dosage :
  - Mean initial : 3.9 mg/kg/d
  - Mean final : 1.6 mg/kg/d
- Mean duration of treatment : 8.2 years (5.9-17 y).
- Mean follow-up period :
  - 10.2 years (5-19 y)
  - 28 patients (40.8%) had more than 10 years of follow up
- CsA discontinued in 10 / 49 patients :
  - Due to prolonged disease inactivity
  - No relapse
  - Prolonged remission in 8 cases
  - Degenerative CME in 2 cases
  - Mean duration of CsA : 8.5 y (4-17 y)
  - Mean follow-up after CsA discontinuation : 6.6 y (4.5-9 y)

Macular edema

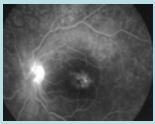
	Initial	Final
NCME	21 (21.4%)	12 (12.2%)
CME	70 (71.4%)	19 (19.4%)

Macular oedema decreased significantly P<0.001

FA : Regression of macular oedema (3 years of follow-up)



20/80



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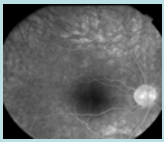
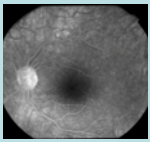
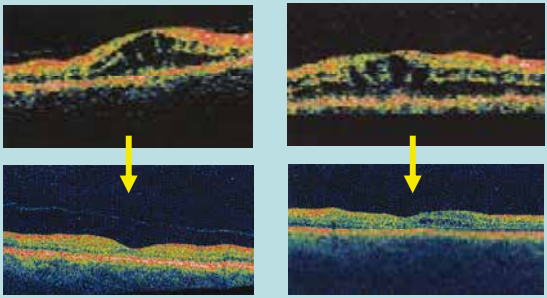


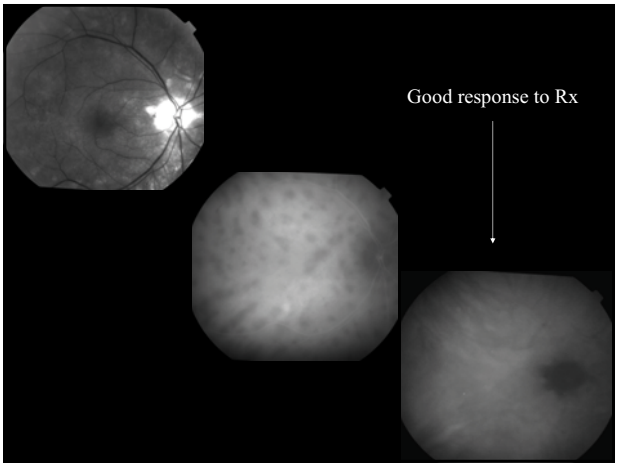
20/20

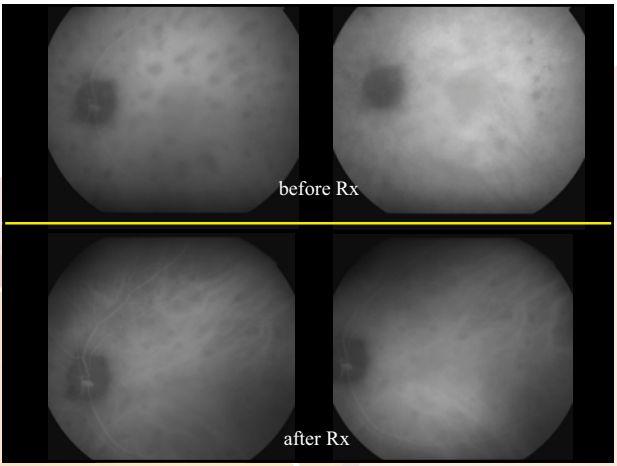


20/20

OCT : Regression of macular oedema (3 years of follow-up)




Good response to Rx


before Rx
after Rx

Major side effects

- Long-term CsA Rx (5 mg/kg/d)
  - High Prevalence of hypertension :
    - High blood pressure : 78% patients after 12 months ($p<0.0001$)
  - Significant renal impairment
    - Significant decrease in creatinine clearance observed in all cases : mean 17.6% (12.4-24.5%) ($p<0.0001$)

Discussion 1

- Initial characteristics of our study-population :
  - Similar to those reported in previous series
  - Caucasian (100%)
  - Affects middle aged people
  - Equilibrated sex-ratio

  (→Priem and Oosterhuis, Br J Ophthalmol. 1988)
- Efficacy of CsA reported in previous series :
  - (→ Nussenblatt *et al.* Am J Ophthalmol. 1983)
  - (→LeHoang *et al.* Transplant Proc. 1988)
  - (→Vitale *et al.* Ophthalmology, 1994)
- Previous studies :
  - Initial, mid-term and long-term efficacy of CsA
  - Small cohort
- First study to evaluate a renal follow up period after CsA discontinuation :
  - Prolonged remission (8 / 49 cases; 16%)

Discussion 2

- Nephrotoxicity and hypertension :
  - Serious side-effects
  - Well established in a single-center prospective cohort study
  - Occur during the first 3 months of therapy
  - Become maximal after 12 months
  - Remain stable for the next few years
- Nephrotoxicity :
  - Dose dependent
  - Highest doses (>3 mg/kg/d) induces more severe alterations than the lowest doses
  - Tapering of CsA doses may improve renal function (only in the absence of interstitial fibrosis)
- Hypertension :
  - Independent of CsA dosage

(→Isnard Bagnis *et al.* J Am Soc Nephrol. 2002)

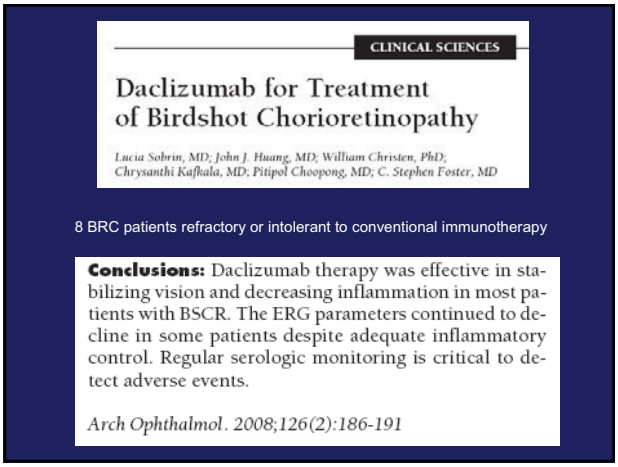
Discussion 3

- 28 patients
- Mean follow-up : 81 months
- 93% were treated with CsA
- 68 % were treated with a combination of azathioprine and CsA
- At the end of the follow-up :
  - 85% of patients had either the same or improved VA
- Encouraging results
- By using this strategy, the preservation of visual function may be obtained

(Kiss *et al.* Ophthalmology, 2005)

- 11 patients (Aza, MTX, CyA, MMF, IvIg : 5 cases)
- Median follow-up : 6 years
- Reduction or stabilization of inflammation in all cases

(Becker *et al.* Ocular Immunol Inflam, 2005)



CLINICAL SCIENCES

Daclizumab for Treatment of Birdshot Chorioretinopathy

Lucia Sobrin, MD; John J. Huang, MD; William Christen, PhD; Chrysanthi Kafkala, MD; Pitipol Choopong, MD; C. Stephen Foster, MD

8 BRC patients refractory or intolerant to conventional immunotherapy

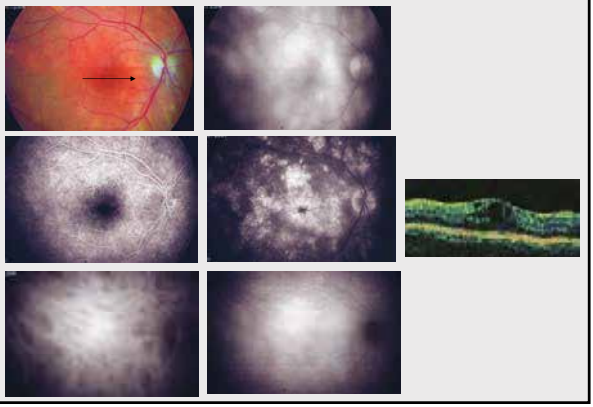
Conclusions: Daclizumab therapy was effective in stabilizing vision and decreasing inflammation in most patients with BSCR. The ERG parameters continued to decline in some patients despite adequate inflammatory control. Regular serologic monitoring is critical to detect adverse events.

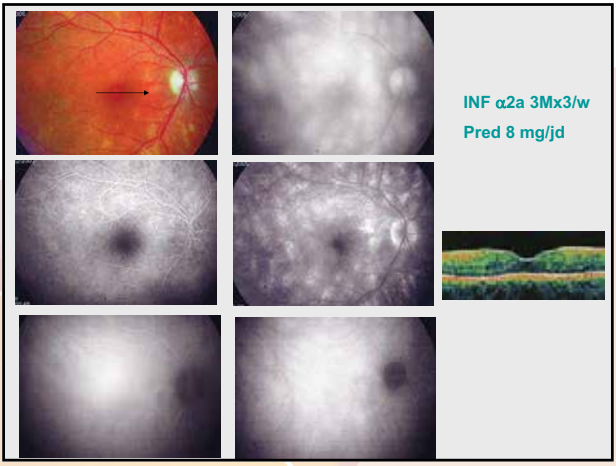
Arch Ophthalmol. 2008;126(2):186-191

Contribution of INF α2a treatment in Birdshot retinochoroïdopathy management

- **Pilot study including 20 patients**
- **Birdshot RC with ME and a prednisone daily threshold > 0.3mg/kg**
- **Criterias compared at ME relapse time , at 6 and 12 months :**
  - **OCT central foveal thickness**
  - **Steroid sparing effect**
  - **BCVA changes**
  - **Fluorescein leakage at 10 mns**
  - **ICGA hypofluorescent nodular lesions at 10 mns**
  - **Therapeutic side effects**

Birdshot RC F 51 y CME TT= prednisone 18 mg/j





Contribution of INF a2a treatment
in Birdshot retinochoroïdopathy management

	OCT CFT	Daily prednisone Threshold	FA leakage	ICGA nodular lesions
Initial time	327±70	34±18	34/34 (100%)	25/32 (78%)
At 6 months	223±62	15±13	11/34 (32%)	8/26 (30%)
At 12 months	211±49	11±9	5/24 (20%)	5/20 (25%)
P	0.001	0.001	0.01	0.01

Conclusion

- BRC : often considered as a chronically progressive disease resistant to treatment
- Long-term preservation of visual function is attainable
- Visual prognosis of active BRC is poor without Rx
- Therefore, an aggressive approach should be proposed early !
- Further randomized multicenter studies are required

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NOTES

Retinal vasculitis: general considerations and differential diagnosis

16

Manfred Zierhut, Germany

MCQ's

Intermediate uveitis can be associated to all listed disorders besides one:

- ❑ sarcoidosis
- ❑ tuberculosis
- ❑ toxoplasmosis
- ❑ TINU Syndrome
- ❑ Multiple Sclerosis

Behcet´s Disease is characterized by all of the following signs besides one:

- ❑ intermediate uveitis
- ❑ retinal infiltrations
- ❑ retinal occlusive vasculitis
- ❑ anterior uveitis
- ❑ optic disc atrophy

In case of retinal vasculitis the following disorders may be underlying disorders besides one:

- ❑ lupus erythematosus
- ❑ multiple sclerosis
- ❑ ankylosing spondylitis
- ❑ tuberculosis
- ❑ sarcoidosis

Inflammation involves retinal vessels mostly as a complication of uveitis, here especially intermediate and posterior uveitis, but can be also a disorder without additional uveal inflammation. The presentation will give thoughts about an improved nomenclature, taking in account clinical and fluorescence-angiographic findings, and also possible associated disorders. The differential diagnosis is mostly based on the underlying disease e.g. intermediate uveitis (often associated with multiple sclerosis or sarcoidosis) or posterior uveitis (most often associated with collagenoses, Behçet's disease or granulomatous disorders).

Manfred Zierhut
Centre of Ophthalmology, University of Tuebingen, Germany

Behcet's disease
Ilknur Tugal-Tutkun, Turkey
17

MCQ's

Based on the current diagnostic criteria for Behçet's disease, which is not considered a diagnostic criterion?

- ❑ Recurrent oral ulcers
- ❑ Recurrent genital ulcers
- ❑ HLA-B51 antigen positivity
- ❑ Positive pathergy test

Which ocular finding is not compatible with Behçet's uveitis?

- ❑ Endothelial dusting
- ❑ Iris nodules
- ❑ Posterior synechiae
- ❑ Vitreous haze

Which statement is wrong about hypopyon seen in patients with Behçet's disease?

- ❑ A marked ciliary injection may not be present
- ❑ It is not sticky and shifts freely with head positioning
- ❑ It is seen in more than 50% of the patients
- ❑ It is usually associated with posterior segment inflammation

Behçet's uveitis has the following characteristics except one :

- ❑ When it is anterior it typically has a high number micro-mutton-fat KPs (keratic precipitates) on the corneal endothelium
- ❑ Can present as an anterior uveitis with hypopyon
- ❑ Very often presents a retinal vasculitis (periphlebitis) that needs to be followed with fluorescein angiography
- ❑ If posterior uveitis is present aggressive therapy is necessary often including systemic corticosteroids, immunosuppressive agents and/or biological agents.

When it was first described as a distict entity in 1937, Behçet's disease (BD) was defined as a triple symptom complex of recurrent oral ulcers, genital ulcers, and uveitis. We now know that Behçet's disease is a complex inflammatory disorder with diverse manifestations. The strong association of Behçet's disease with the HLA-B51 antigen has been known for more than 3 decades. This was confirmed by the recent genome-wide association studies which have also shown that there are several shared genetic factors throughout the old Silk Route. Inflammatory disease manifestations are thought to develop as a result of interactions between genetic variations and environmental factors, mainly commensal microbes.

Patients with Behçet disease have recurrent inflammatory attacks in all organ systems involved. There is no specific diagnostic test. The diagnosis is based on a combination of clinical findings, including recurrent oral ulcers, genital ulcers, skin lesions, eye lesions, and a positive pathergy test. More than 50% of the patients have ocular involvement, typically in the form of nongranulomatous panuveitis and retinal vasculitis with a relapsing and remitting course. The onset of uveitis is in the third or fourth decade of life in the majority of the patients. Uveitis is more frequent and its course is more severe in male patients. The typical findings of uveitis attacks include anterior chamber cells with or without a hypopyon formation, diffuse vitreous haze, occlusive periphlebitis, retinal infiltrates, and inflammation of the optic disc. In severe attacks, diffuse retinal edema and even a serous retinal detachment may develop. Macular edema is the most common complication. Recurrent attacks lead to permanent loss of useful vision due to optic atrophy, maculopathy, and diffuse atrophy and gliosis of the retina. Fluorescein angiography is the gold standard in monitoring disease activity. Anterior chamber flare measured by laser flare photometry correlates with fluorescein leakage in the posterior segment.

Management of Behçet's uveitis is based on the rapid control of intraocular inflammation and prevention of recurrences. Corticosteroids are generally used for the treatment of acute attacks. However, patients with posterior segment involvement require long-term immunomodulatory treatment in order to prevent recurrences. Both azathioprine and cyclosporine have been shown to be effective in controlled trials. Interferon alfa or anti-TNF agents are used in resistant cases. Visual prognosis has improved with the introduction of biologic therapy for this potentially blinding disease.

Ilknur Tugal-Tutkun
Istanbul, Turkey

MCQ's

Local therapy with steroids in uveitis

- ❑ Is always the first line of therapy
- ❑ It is not associated with the development of cataract and glaucoma
- ❑ Leads to resolution of macular edema in nearly all cases
- ❑ It should not be used in cases of infectious uveitis

Anti-VEGF drugs

- ❑ Have no role in the management of complications of uveitis
- ❑ Are associated with the same complications as in local steroid therapy
- ❑ May be an option in cases of chronic macular edema
- ❑ Can be used as monotherapy in cases of active uveitis

Intraocular slow-release devices

- ❑ Retisert is not frequently associated with cataract and glaucoma
- ❑ Ozurdex is a good option for the treatment of CME in toxoplasmosis
- ❑ Represent a good alternative in unilateral cases of non-infectious uveitis
- ❑ Can be used in cases of steroid-induced glaucoma

The management of non-infectious posterior uveitis remains a challenge for the uveitis specialist. Steroids are the mainstay of therapy and may be delivered as a periocular injection or given systemically. The systemic route, used in bilateral cases, especially those associated with an underlying systemic disease, requires the use of high dose of steroids, since many barriers need to be overcome before the drug can reach the site where it will exert its action. The addition of steroid sparing agents is frequently necessary because of the high level of steroids needed to control the inflammation, or because of unacceptable side effects. The use of such drugs will undoubtedly have an impact on the quality of life due to the many potential side effects and the need for constant monitoring. Some of the events may be life threatening.

In unilateral or asymmetric cases the use of periocular injections can be attempted as a first line of therapy, as long as the formal contraindications have been observed. This approach allows the delivery of the drug in close proximity to the eye, with intraocular penetration of the drug occurring by diffusion through the sclera, and eliminating systemic side effects. More recently, intraocular delivery of the drug has become another interesting alternative, overcoming all barriers and putting the drug exactly where it is needed. An on going trial is studying the benefit of a slow-release device and many reports have addressed the use of intra-ocular injections of triamcinolone acetonide to treat posterior uveitis.

Periocular Injections

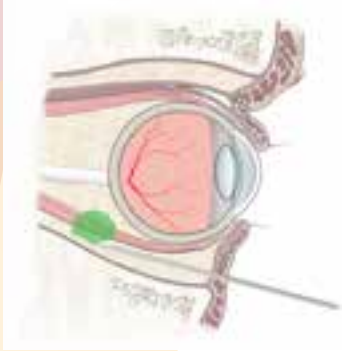
Two types of injections are frequently used: the orbital floor injection (OFI) and the posterior sub-Tenon's injection (PST). The most frequently used steroid preparations are aqueous suspension such as triamcinolone, and long-acting depot such as methylprednisolone. Triamcinolone acetonide 40mg in 1ml seems to be the preferred type.

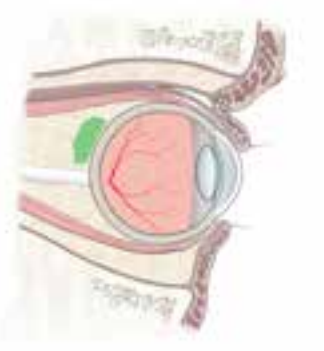
The OFI injection is carried out using a long 25G needle in the same way that peribulbar anaesthetic in applied. It has the advantage of being safer, especially for beginners, but will put the drug outside the muscular cone. Since the penetration is by diffusion, as mentioned above, this location means that the drug is further away from the eye and it is likely that less of the drug will penetrate into the posterior cavity.

The PST injection is performed with a short 25G needle, using the technique originally described by Nozik. The supero-temporal approach is the preferred one and following good anaesthesia of the conjunctiva, the needle, with bevel down, is advanced posteriorly with a gentle lateral movement, essential to detect any contact with the sclera that may result in perforation of the globe. It is more dangerous and feared

by beginners, but once mastered can be used with confidence, delivering a larger concentration of the drug adjacent to the posterior sclera.

PST injection technique according to Nozik (1972)





OFI PST

Location of the drug in relation to the globe.

The injections are usually attempted up to three times with an interval of 4 to 6 weeks in case of no response. In cases of a positive response, another injection will be necessary whenever symptoms recur, which will usually be 4 to 6 months. This is certainly variable and shorter and longer periods may be observed.

The main contra-indications are the presence of an active intra-ocular infection and a history of increased intra-ocular pressure induced by exposure to topical steroids.

The complications include:

- Globe penetration
- Elevation of IOP
- Cataract formation
- Scarring
- Ptosis
- Sub-dermal fat atrophy
- Extraocular muscle paresis
- Optic nerve injury
- Retinal and choroidal vascular occlusion

Intra-vitreal triamcinolone injection (IVTA)

The use of triamcinolone acetonide at a concentration of 4mg in 0.1ml, has become quite a popular option in the management of many conditions (Refractory pseudophakic macular oedema, macular oedema in central retinal vein occlusion, vitreo-retinal procedures and AMD), but its use, as in periocular injections, is off-label, and there is no real evidence for its use.

A study of the pharmacokinetics of the drug following a single injection of 4mg of triamcinolone acetonide in 0.1ml, showed that the mean elimination half-life was of 18 days in non-vitrectomised eyes, with a half-life of 3 days in vitrectomised eyes. Measurable concentrations were found for approximately 3 months (non-vitrectomised eyes).

The mechanism by which cystoid macular oedema is treated is unclear. The response is too fast for a response due to control of inflammation, and it is possible that other

mechanisms such as inhibition of lipid peroxidation and hydrolysis, as in spinal cord injury, are playing a role.

The list of potential complications include:

- Endophthalmitis
- Ocular hypertension
- Cataract
- Haemorrhage
- Retinal detachment

Ocular hypertension is the most frequently observed problem, with post series reporting moderate increases in intra-ocular pressure (IOP), with good response to topical therapy and a duration of the effect for about 6 months. It is important to note that most of this data comes from injections given in patients without a history of uveitis. Uveitis patients are more likely to have problems with steroid-induced pressure (trabeculum exposed to chronic inflammation and previous steroid use), and in these patients it may show higher levels and be harder to control.

An important point to be considered is the effect of repeated injections. Most of the experience reported is related to a single injection, and it is clear from experimental work that the complications increased after the first injection. Also, many centres are using different concentrations of the drug (up to 25mg), but there is some doubt about the precise concentration and the long-term consequences.

Apart from the feared infectious endophthalmitis, sterile endophthalmitis has also been reported. Bacterial endophthalmitis after IVTA injection may present in an atypical, relatively delayed manner with decreased vision but no pain or redness

Presumed noninfectious endophthalmitis presents within 2 days after the injection, may be accompanied by discomfort, and has a hypopyon that may be the triamcinolone material itself (pseudo-endophthalmitis) or a sterile inflammatory reaction.

It seems that toxicity of components of the vehicle, especially benzyl-alcohol, is responsible for the latter. Attempts to decant or filter the drug may result in higher concentration of the toxic agent since it seems to have a strong affinity for the triamcinolone crystals.

In summary:

- Periocular triamcinolone remains an important alternative in the management of CMO associated with non-infectious posterior uveitis, especially in unilateral or asymmetric cases, avoiding systemic side effects.
- Intra-ocular triamcinolone is a potent alternative in more resistant CME, but more data on toxicity and side effects in repeated use is still needed.
- Combined use of both techniques may be a good option is some patients.

Anti-VEGF agents

VEGF is involved in the pathogenesis in uveitis, being markedly increased in the aqueous humor of patients with anterior uveitis and CMO. The levels found in the vitreous are similar to those found in AMD patients, but much lower than in diabetes.

Most reports available are on Bevacizumab for the treatment of recalcitrant CMO and some have showed some OCT improvement in 1-2 weeks after 1 single injection of 2.5mg, while other results were more variable. The effect is transient and repeated injections become necessary. No significant systemic side-effects have been reported, but Ranibizumab has been associated with subsequent development of uveitis from 0.7 to 1.3%. It represents an alternative in patients who present an elevation of intraocular pressure when treated with steroids and who are unwilling to take systemic drugs or are unsuitable for systemic therapy. This strategy can also be used for the treatment of CNV complicating a uveitic condition, most frequently seen in PIC, multifocal choroiditis, but a possibility complicating any condition that interferes with integrity of Bruchs/RPE structure.

Devices

The use of a slow-release intraocular devices is currently being investigated. One device (**Retisert**) uses Fluocinolone acetonide (a synthetic derivative of Triamcinolone acetonide), which is released at a constant rate for up to three years. This device is the first to be licensed by the FDA for use in posterior non-infectious uveitis. **Retisert** is implanted via a pars-plana approach along the same lines as the Vitrasert used for the treatment of CMV retinitis. The incision is smaller (3.5mm) and the strut should be anchored to the sclera with 8-0 Prolene, while the scleral wound is sutured with

9-0 Prolene, which allows the knots to be properly buried into the sclera. The use of Prolene and not Nylon, as in the Vitrasert, is due to the fact that the implant will last for about 2 and a half years and with Nylon there is a risk of suture degradation and potential gaping of the wound, which will not heal properly due to the constant release of a steroid inside the eye. The results of pivotal trials have shown a significant reduction in recurrences when compared to standard of care, but there was a high incidence of complications such as cataract in nearly 100% of patients and high intraocular pressure, requiring filtering procedure in nearly 10% of the cases. This device was approved last year by the FDA for use in non-infective posterior uveitis in the USA.

Other forms of intraocular devices include **Iluvien**, with fluocinolone acetonide, **Osurdex(R)**, with Dexamethasone, and **SurModics I-vation(TM)** TA Intravitreal Implant.

Iluvien has been licensed for the treatment of diabetic macular oedema and trials on its use for the treatment of uveitis are about to start. Phase 3 clinical trials are ongoing for the use of fluocinolone acetonide implant to treat non-infectious posterior uveitis (PSivida).

Ozurdex has been licensed for the treatment of macular oedema in uveitis. The Huron study was a prospective, multicenter, masked, randomised, parallel group clinical trial

Patients were randomised (stratified by baseline vitreous haze) using a 1:1:1 allocation to a single treatment with DEX DSS 700 µg, DEX DSS 350 µg, or sham (needleless applicator). A total of 229 patients were enrolled. There was a significant difference in those achieving zero vitreous haze and having improvement of vision of 15 letters or more on the Ozurdex groups comparing to sham. Intraocular pressure rise was significant in these groups comparing to sham, but there was no increase in the use of pressure-lowering medication.

The problems with all steroid devices are similar and mostly related to development of cataract and high intraocular pressure.

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NOTES

Management strategies for chronic uveitis

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19

Outline not received

NOTES

MCQ's

Cyclosporin A is

- ❑ A fusion protein
- ❑ A monoclonal antibody
- ❑ A calcineurin inhibitor
- ❑ None of the previous answers

Mycophenolate mofetil:

- ❑ is metabolised in the liver to the active moiety mycophenolic acid
- ❑ is a calcineurin inhibitor
- ❑ cannot be used in uveitis
- ❑ is a monoclonal antibody

Adalimumab:

- ❑ Is a receptor-IgG fusion protein
- ❑ Is a chimeric monoclonal antibody
- ❑ Is a phage display derived therapeutic antibody
- ❑ None of the previous answers

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. Immunosuppressive therapy for severe, sight-threatening, intraocular inflammation can be considered the mainstay of treatment of non-infectious uveitis.

This therapeutic strategy is generally characterized by 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 leads a certain number of side effects, such as high blood pressure, high blood sugar, cataract and glaucoma. For such reasons, immunotherapy is often introduced. An increased understanding of the mechanisms of non-infectious uveitis has expanded the knowledge on the potential control of ocular immune response. Therefore, several immunosuppressants have been proposed for the control of sight-threatening uveitis (Figure 1).

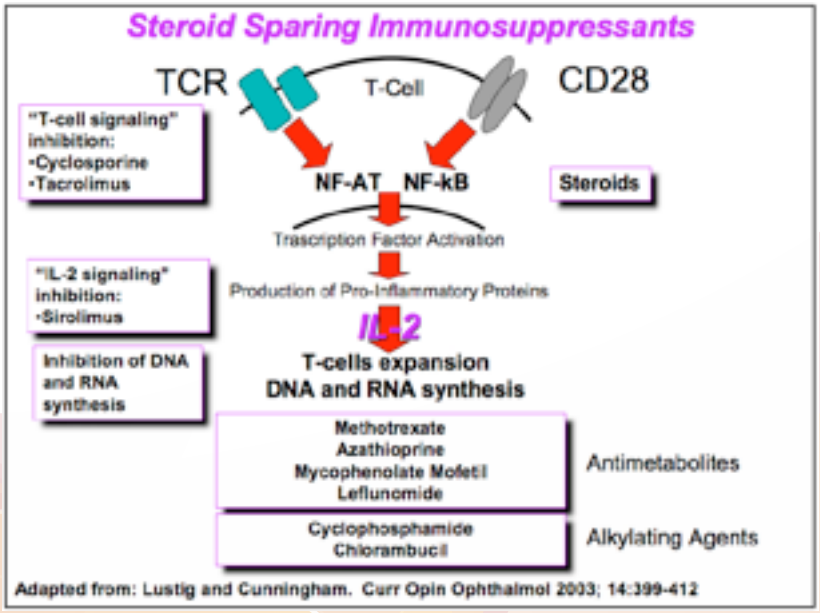

Figure 1

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].

MMF is classified as 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 lead the modern approach towards a new category of drugs called biologics. This type of immunesuppressors represents a copernican 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).

Albeit several biologic targets have been identified, anti-Tumor Necrosis Factor (TNF)-α blockers represent the most promising molecules used in the treatment of severe sight- threatening 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 (TNF-R) 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]

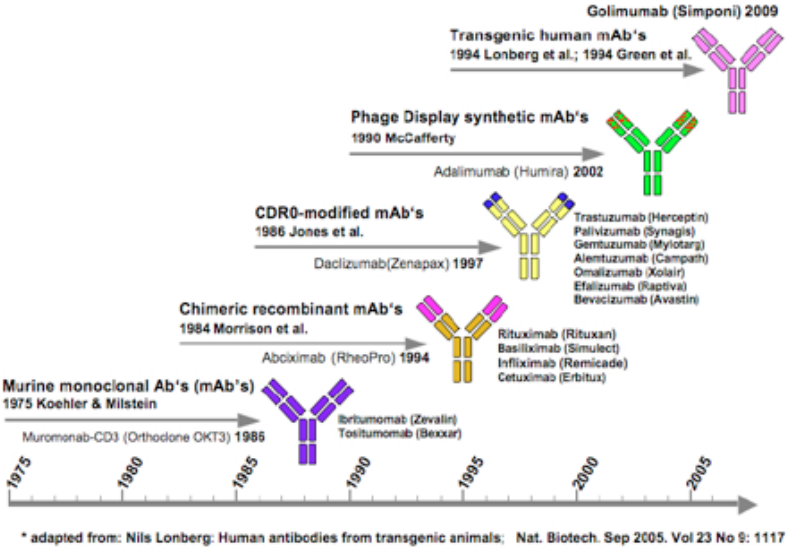

Figure 2

TNF-α plays a key role in the pathogenesis of many inflammatory diseases (Figure 3): 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 actually not recommended in inflammatory diseases associated with uveitis, because

this is considered a potential trigger of "ex novo" uveitis and this can even exacerbate uveitis itself [29].

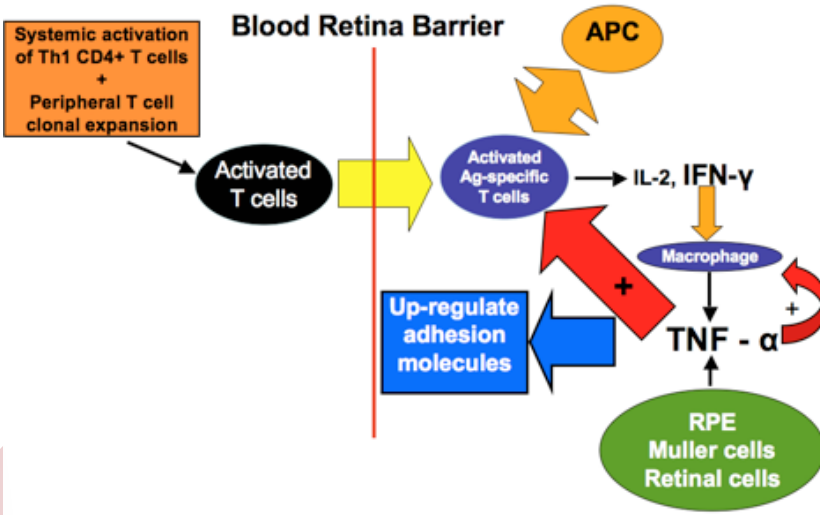

Figure 3

Dick et al. [30] showed that TNF-α inhibition with a p55 TNF-α receptor fusion protein (TNFr-Ig) reduces interferon (IFN)-γ 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.

Even though 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-TNF-α 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.

Other biologic agents have been tested for non-responder uveitis, even though the data in the medical literature is limited. One of these monoclonal antibodies is Rituximab (Rituxan®, Roche, Basel, Swiss), which is a CD20-directed mouse-human chimeric monoclonal IgG1 antibody approved by the Food and Drug Administration in 1997 for treatment in relapsing or refractory non-Hodgkin lymphoma [38]. Rituximab has been successfully used in scleritis associated with Sjogren's syndrome and Wegener's granulomatosis [39,40]. Despite its B-cell-driven action, this evidence of its efficacy in predominantly T cell mediated autoimmune disease suggests a possible role in the treatment of refractory uveitis. Some data in the literature already suggests that rituximab may be effective for the treatment of Bechet Disease-related conditions. A randomized controlled study showed a better disease control in the rituximab group compared to the cytotoxic combination therapy group with ocular inflammation significantly improved in both groups [41]. Rituximab may also act as rescue therapy in severe JIA- associated uveitis unresponsive to traditional immunosuppressive agents and TNF-α inhibitors [42]. This drug is administred by intravenous infusions but also has been used intravitreally to treat primary intraocular lymphoma, based on its efficacy in systemic lesions [43]. The use of rituximab for treatment of primary intraocular lymphoma showed initial response with clearance of the vitreous without retinal toxicity, even though there is a lack of long-term results on this procedure [44].

Alemtuzumab (Campath®, Genzyme, Naarden, Netherland) is a humanized anti-CD52 cytolytic antibody indicated for the treatment of B-cell chronic lym¬phocytic leukemia. This drug seems to be an effective treatment in refractory uveitis with long term remission [45]. The main concern is represented by the evidence that Alemtuzumab led to a prolonged CD4+ T cells deficiency after the treatment, exposing patients to the risk of severe, opportunistic infections [46].

Abatacept (Orencia®, Bristol-Myers Squibb, New York City, USA) is a soluble fusion protein composed of a fragment of human immunoglobulin and the ligand-binding domain of cytotoxic T-lymphocyte-associated antigen-4. Data on its use in uveitis are limited to case reports and case series, although promising results have been shown in the treatment of refractory JIA-related uveitis [47-49]. On the other hand, larger series with long term follow up of this drug in paediatric uveitis is essential to prove his efficacy.

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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NOTES

MCQ's

An appropriate strategy in a patient with uveitis and a retinal detachment would be:

A - Do a work-up for the cause of uveitis
B - Adjust immunosuppression pre and post op
C - Identify the cause of the detachment and its relationship to the site of inflamma-tion/infection
D - Vitrectomy - buckle - cryotherapy
E - Decide on surgical course in the operating room
F - Use minimal surgery to minimize post-op inflammation

- ❑ C - A - B - E
- ❑ C - B - D
- ❑ C - A - B - F
- ❑ C - B - F
- ❑ C - B - E

In patients with intraocular lymphoma, the diagnostic vitrectomy:

- ❑ Is often the initial means of confirming the diagnosis and can be considered as a first line investigation.
- ❑ FACS scanning and microdissection insure a high diagnostic yield and supplant other techniques.
- ❑ Repeat vitrectomies are rarely needed
- ❑ A full diagnostic evaluation is required in all cases of diagnostic vitrectomy
- ❑ all of the above

Vitreo-retinal surgery in jnvenile idiopathic arthritis requires:

- ❑ extensive with vitreous base dissection and lens removal in all cases
- ❑ should be limited to the pathology identified pre-operatively (macular pucker, hypotony, serous RD)
- ❑ core vitrectomy is required in all cases of cataract surgery
- ❑ should be avoided given poor outcomes from surgery
- ❑ none of the above

Introduction:

Surgery may be called upon during the management of uveitis patients to either establish a diagno-sis or to manage vitreoretinal complications of the posterior pole. These can arise as a direct result of the inflammatory process or be concurrent but not directly related (say for example a retinal detachment due to a tear outside of an area of retinitis).

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 to cover vitreoretinal procedures. At the completion of surgery, pa-tients 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 ster-oid responder. For patients whose retinal involvement is infectious in origin, the timing of surgery will vary based on etiology, response to therapy, the severity of the ocular inflammation and to which degree vital ocular structures are threatened.

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 imme-diate ocular problem, but prevent future complications. Treatment with anti-infective agents on the basis of a presumed diagnosis is often indicated particularly in cases where retinal necrosis is sus-pected, as time is of the essence. Delay in accessing the operating room should never be a reason to delay therapy when vision is threatened.

VR for diagnostic indications:

When vision is threatened in both eyes by progressive disease, it may be necessary to obtain an ocu-lar sample to establish the cause and decide on the most appropriate therapy. The least invasive approach likely to yield a diagnosis should be chosen. As an initial step, you should first consult with pathology and microbiology. It is important that they understand how small your sample will be, and what the differential is likely to be. Given the size, only limited investigations are possible. The challenge then, is to start these in an appropriate framework. It is also important that you get enough tissue for a diagnosis to be possible. Even in the cases of ocular lymphoma, a minimum of about 50 lymphomatous cells are required using molecular techniques to confirm the diagnosis. Under certain circumstances, it will be possible for a technician to come to the operating room and confirm that the sample is sufficient. Your tissue

is precious and should be brought to the pathology lab in person for processing, and this should be done immediately.

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. Mostly, transretinal biopsies are appropriate. Beware that to minimize tissue damage, it is best to "aspirate the biospy through a 20G needle, the needle protects the edges of the tissue.

In all cases, the sample obtained should be used to gain maximum yield. Cytology can give you an idea of cell type, FACS analysis will tell you of the distribution of particular cell populations (for example in lymphoma or cancer), microbiology informs you of the presence of an infection either by direct culture or by PCR, a Goldman Witmer quotient on vitreous fluid indicates the type of antibodies being generated intraocularly. A combination of techniques can help to improve the diagnostic yield. Note that even a Giemsa stain can give you information: 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 (including relatively mild forms of pars pla-nitis). Removal of the vitreous reduces the burden 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 all traction in the macular area is important. In children, given the propensity to form epiretinal membranes, peeling of the ILM is probably indicated. While the ede-ma decreases in the immediate postoperative period, it often recurs later. Use of local (periocular or intraocular steroids) for long term remission is in some cases needed. Altermatively, intraocular methotrexate is also efficacious. Newer intraocular immunosuppressives still require investigation but probably can also be considered. [7-12]

Vitrectomy for retinal fibrosis (ERM, hypotony):

Epiretinal membrane formation is not uncommon in uveitis patients and can develop following previous vitrectomy or following vitritis secondary to infections such as toxoplasmosis. Epiretinal membranes in this setting are often multi-layered and may require repeat staining of the affected area to be removed. One should take particular care in children where such membranes can devel-op into a gliotic scar. These should be addressed surgically before such a stage develops. [13]

Hypotony results for incomplete vitrectomy carried out in the anterior portion of the vitreous cavi-ty. 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. Residual vitreous will condense on the posterior surface of the iris and over the ciliary processes leading to progressive atrophy of the cili-ary epithelium. When the atrophic process is not complete, this fibrotic tissue needs to be removed from the pars plicata over an extensive area if the visual function and the eye are to be preserved. [14]

Management of retinal detachments in uveitis:

Retinal detachments are relatively rare in uveitis patients occurring in about 1% of patients. 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 detachment. The latter occurs 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. Wait until the retinitis is clearly responding to therapy and there has been no further progression of the necrosis. A detachment usually takes a few weeks to develop, so you have some time. It is due to vitreous contraction, hence in the absence of severe vitritis, it is much less likely. In these cases, a good laser barrier may be sufficient.

The prognosis with retinal detachments in uveitis patients depends on the severity of inflammation. In a quiescent eye, the prognosis should be the same as for any other detachment surgery. In eyes with active inflammation, prognosis is usually poor. One should minimize inflammation (laser ra-ther than cryo, and vitrectomy rather than encirclement). Liberal use of silicone oil is also advised in the presence of active inflammation as the oil will also act as an "insulator", preventing mem-branes 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 preferably with indentation prior to any surgery. [15,16]

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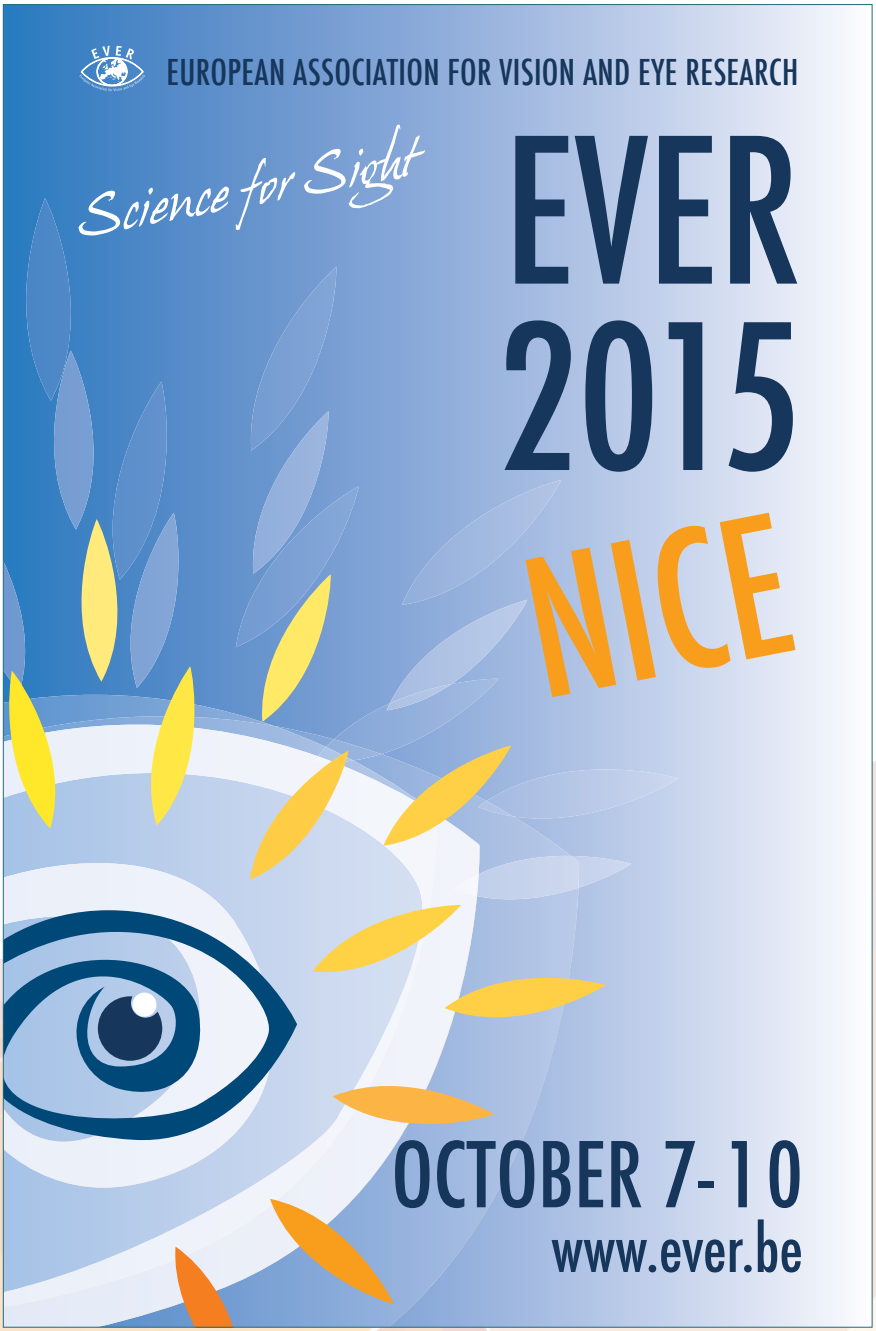
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MCQ answers

Page 11 - Gerhild Wildner

- What is the role of T helper cells?
  To help B cells and cytotoxic T cells
- What are pattern recognition receptors?
  Receptors on innate immune cells recognizing pathogens or dead cells
- What is necessary to maintain the immune privilege of the eye?
  Spleen and eyes

Page 15 - Stephan Thurau

- In which clinical situation is the PCR method useful?
  Prove of monoclonality of lymphoma from vitrectomy specimen
- Which statement about the Goldman-Whitmer-coefficient is correct?
  Comparison of specific IgG to total IgG in ocular and serum.
- In which situation is serologic testing most useful for the diagnosis of uveitis?
  Syphilis test in unclear uveitis

Page 17 - Carl Herbort

- The following statements about the fluorescein sodium molecule and fluorescein angiography are correct except one

  .....

- The following propositions are true for the ICG molecule or ICG angiography except one

  .....

- The following propositions are true for angiography and OCT in inflammatory diseases except one

  .....

Page 27 - Graham Holder

- The most sensitive ERG parameter in birdshot chorioretinopathy is:
  The photopic 30Hz flicker ERG
- Melanoma associated retinopathy is associated with:
  Global loss of retinal On-pathway function
- AZOOR is usually associated with:
  Delayed photopic 30Hz flicker ERG;

Page 29 - Nicholas Jones

- Select one most appropriate answer from the following:
  Iris nodules are most commonly seen in eyes with Fuchs' heterochromic uveitis

Statements about infective anterior uveitis:

- Cytomegalovirus can cause anterior uveitis without retinitis, even in the immunocompetent - true
- Any treated intraocular infection can be followed by chronic non-infective anterior uveitis - true
- Tuberculosis never causes anterior uveitis alone, without posterior segment involvement - false
- Chronic anterior uveitis with sectorial iris atrophy is typical of HSV-1 - true
- If syphilis involves the anterior segment, inflammation is always granulomatous in appearance - false

When managing severe acute anterior uveitis:

- A positive syphilis ELISA with an RPR of 1:4 indicates active syphilis - false
- Phenylephrine should not be used to dilate the pupil - false
- Sub-conjunctival steroid injection is ineffective if the patients is using hourly prednisolone acetate - false
- If the posterior pole can be seen to be normal, there will be no retinitis - false
- Any posterior synechiae should be broken on the first day of presentation if possible - true

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Page 43 - Arnd Heiligenhaus

- The differential diagnosis of JIA associated uveitis does not include:

  .....

- Uveitis risk factors and uveitis screening in JIA patients. What is correct?

  .....

- Therapy of oligoarthritis associated uveitis. What is correct?

  .....

.....

Page 49 - Bahram Bodaghi

- All of the following diseases may be associated with an herpes virus infection except
  Fuchs uveitis
- All of the following are classical manifestations of herpetic viral uveitis except
  Extensive posterior synechiae
- Treatment of acute HSV-1 associated anterior uveitis does not include
  Topical acyclovir ointment

.....

Page 71 - Carlos Pavésio

- Regarding ocular Toxoplasmosis:
  Systemic steroids should only be used alongside anti-toxoplasmic drugs
- Toxocara ocular infections:
  May result in vision loss by directly affecting the posterior pole
- Diffuse Unilateral Sub-acute Neuroretinitis (DUSN)
  Yellow lesions disappear and leave pigmentary changes

.....

Page 85 - Philippe Kestelyn

- Which statement is true concerning ocular syphilis:
  Ocular involvement in secondary syphilis often follows months after the systemic manifestations (e.g. skin rash)
- Which statement concerning the diagnosis of ocular syphilis is true?
  The presence of specific anti-treponemal antibodies in cerebrospinal fluid is no proof of neurosyphilis
- Advantages of the IGRA test in the diagnosis of TB includes the following:
  No cross-reaction with antigens from BCG vaccine

.....

Page 97 -Bahram Bodaghi

- Viral retinitis

  Is an absolute emergency
- Clinical manifestations of ARN syndrome does not include

  Relapses in the same eye
- CMV retinitis

  Must be treated with oral valgancyclovir

.....

Page 117 - Per Montan

- What signs and symptoms would make you suspect endophthalmitis?

  .....
- What is your first measure when you suspect an endophthalmitis in a patient seeing LP only after previous surgery?

  .....
- What organisms cause the most devestating course of endophthalmitis?

  .....

.....

Page 121 - Phuc LeHoang

- Primary Intra-Ocular Lymphoma is:
  Lethal
- Among the following signs of Primary Vitreo-Retinal Lymphoma, which one is the less frequent:
  Iris posterior synechiae

Page 159 - Manfred Zierhut

- Intermediate uveitis can be associated to all listed disorders besides one:
  toxoplasmosis
- Behcet´s Disease is characterized by all of the following signs besides one:
  intermediate uveitis
- In case of retinal vasculitis the following disorders may be underlying disorders besides one:
  ankylosing spondylitis

Page 161 - Ilknur Tugal-Tutkun

- Based on the current diagnostic criteria for Behçet's disease, which is not considered a diagnostic criterion?
  HLA-B51 antigen positivity
- Which ocular finding is not compatible with Behçet's uveitis?
  Iris nodules
- Which statement is wrong about hypopyon seen in patients with Behçet's disease?
  It is seen in more than 50% of the patients
- Behçet's uveitis has the following characteristics except one :
  When it is anterior it typically has a high number micro-mutton-fat KPs (keratic precipitates) on the corneal endothelium

Page 163 - Carlos Pavésio

- Local therapy with steroids in uveitis
  It should not be used in cases of infectious uveitis
- Anti-VEGF drugs
  May be an option in cases of chronic macular edema
- Intraocular slow-release devices
  Represent a good alternative in unilateral cases of non-infectious uveitis

.....

Page 173 - Piergiorgio Neri

- Cyclosporin A is
  A calcineurin inhibitor
- Mycophenolate mofetil
  is metabolised in the liver to the active moiety mycophenolic acid
- Adalimumab
  Is a phage display derived therapeutic antibody

.....

Page 185 - Marc de Smet

- An appropriate strategy in a patient with uveitis and a retinal detachment would be:
  A: C - A - B - E
  B: C - B - D
  C: C - A - B - F
  D: C - B - F
  E: C - B - E
- In patients with intraocular lymphoma, the diagnostic vitrectomy:

  .....
- Vitreo-retinal surgery in jnvenile idiopathic arthritis requires:

  .....

European University Professors of Ophthalmology

PROGRAMME EUPO 2015

UVEITIS
Friday, 5 June 2015

Uveitis organised by Carlos Pavesio

08.35-10.00	Section 1: Basic concepts
10.00-10.30	Break
10.30-12.10	Section 2: Anterior segment
12.10-13.20	Lunch
13.20-15.00	Section 3: Posterior uveitis 1
15.00-15.40	Section 4: Posterior uveitis 2
15.40-16.00	Break
16.00-16.40	Section 4: Posterior uveitis 2 (cont)
16.40-18.00	Section 5: Therapy

GLAUCOMA
Saturday, 6 June 2015

Glaucoma organised by the European Glaucoma Society
Course coordinator: Carlo Traverso

Session 1: Surgical management
Session 2: Monitoring and Treatment decisions
Session 3: Diagnosis (and impact on Quality of Life)

EUPO Course 2015
June 5-6, Vienna, Austria - inconjunction with SOE 2015