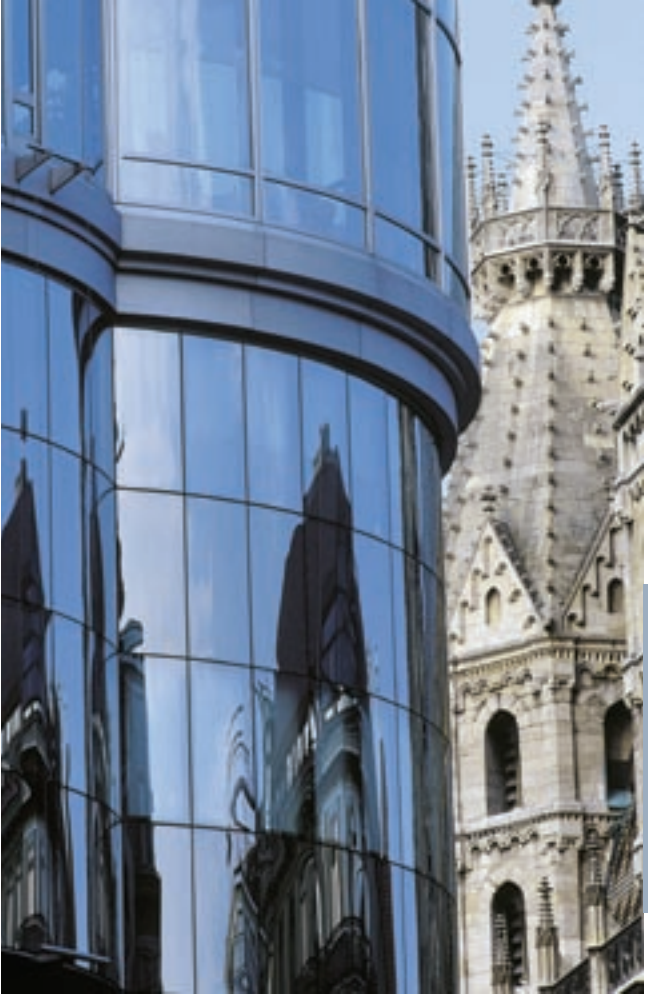

PROGRAMME

9 June

2007

VIENNA

AUSTRIA

EUROPEAN PROFESSORS OF OPHTHALMOLOGY

EUPO COURSE 2007

FOR RESIDENTS IN OPHTHALMOLOGY

UVEITIS

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PROGRAMME

SATURDAY June 9, 2007

08:30 – 10:00 First Morning Session
Basic Concepts
Moderators: James P. Dunn, United States
Marc D. de Smet, Belgium **Page**

08:30 **Immunologic mechanisms**
Gerhild Wildner, Germany

08:52 **Use of histopathology in the management of infectious uveitis**
Narsing Rao, United States

09:15 **Anterior chamber tap and aqueous humor analysis**
Uwe Pleyer, Germany

09:37 **Indocyanine Green Angiography**
Carl P. Herbort, Switzerland

10:30 – 12:00 Second Morning Session
Anterior segment + viral retinitis
Moderators: James P. Dunn, United States
Marc D. de Smet, Belgium Page

10:30 **Fuch's/Posner/HLA B27**
Phillip I. Murray, United Kingdom

10:48 **JCA + paediatric uveitis**
Clive Edelsten, United Kingdom

11:06 **AIDS today (AIDS, CMV)**
James P. Dunn, United States

11:24 **Herpetic ocular disease**
Marietta Karavellas, Greece

11:42 **Scleritis**
Carlos E. Pavésio, United Kingdom

13:15 – 14:00 First Afternoon Session
Posterior Uveitis I
Moderators: James P. Dunn, United States
Marc D. de Smet, Belgium Page

13:15 **Toxoplasmosis and parasitic infections**
Carlos E. Pavésio, United Kingdom

13:26 **Tb and syphilis**
Philippe Kestelyn, Belgium

13:37 **Lyme disease and other zoonotic diseases**
Massimo Accorinti, Italy

13:48 **Lymphoma and mascarade**
Janet Davis, United States

14:30 – 16:00 Second Afternoon Session
Posterior Uveitis II
Moderators: James P. Dunn, United States
Marc D. de Smet, Belgium **Page**

14:30 Intermediate / pars planitis
Pierre Labalette, France

14:52 Birdshot retinochoroidpathy
Phuc LeHoang, France

15:15 Ocular Sarcoidosis
Youssef El-Shabrawi, Austria

15:37 Behçet's disease
Ilknur Tugal-Tutkun, Turkey

16:30 – 18:00 Third Afternoon Session
Therapy
Moderators: James P. Dunn, United States
Marc D. de Smet, Belgium Page

16:30 Use of Corticosteroids in Uveitis
James P. Dunn, United States

16:52 Management strategies for chronic uveitis
Bahram Bodaghi, France

17:15 New therapeutic modalities and monoclonals
Stephan Thurau, Germany

17:37 Surgical management
Marc de Smet, Belgium

Immunologic mechanisms

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Immunologic Mechanisms of Uveitis

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

Antigen recognition, B and T cells

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

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

The immune privilege of the eye

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

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

The blood-retina-barrier (BRB):

Tight junctions of the intraocular endothelia prevent transmigration of non-activated leucocytes, such as T- and B-cells, NK-cells, macrophages and granulocytes. Furthermore, the BRB is impermeable for macromolecules such as antibodies, complement and coagulation factors.

ACAID

ACAID defines the immune privilege of the anterior chamber, but there is a retinal immune privilege as well. Antigens within the eye normally do not activate an immune response, but rather induce tolerance. Intraocular antigens (naturally occurring or experimentally introduced) are transported to the spleen, where antigen-specific tolerance is generated. Special dendritic cells/macrophages (F4/80+) localized in iris and ciliary body can only induce a tolerogenic, but no defensive immune response.

Ocular antigens induce regulatory cells (T cells, NK cells) and production of non-complement-fixing antibodies. Furthermore, iris and ciliary body secrete suppressive factors, such as TGF-β, IL-10, α-MSH and others.

Besides preventing intraocular inflammation, ACAID also helps to accept corneal grafts.

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

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

The blood-retina-barrier as well as ACAID can be overcome by activated leucocytes. They are enabled to penetrate the BRB and are not bothered by the suppressive factors in the eye. However, they have to be activated specifically for intraocular antigens, which are usually sequestered and not accessible to the immune system, as long as the BRB is intact. In case of infectious uveitis the respective pathogen has normally been seen by the immune system in the periphery. Thus, activated lymphocytes with specificity for the pathogen can invade the eye to attack the virus or bacteria. For "autoimmune" uveitis we postulate antigen crossreactivity, "mimicry" of an antigen activating the immune system in the periphery and an intraocular antigen. Those

peripherally activated T cells can cross the BRB and will find an antigen in the eye that resembles the antigen of their original activation. Local reactivation and subsequent secretion of inflammatory cytokines will initiate inflammation such as uveitis. Those "mimotopes" can be provided by environmental antigens such as pathogens or even nutritional antigens (e.g. casein from bovine milk).

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

Use of histopathology in the management of infectious uveitis

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Histopathology is a part of the ophthalmologist s armamentarium that is useful in the diagnosis and management of intraocular inflammation/uveitis in particular infectious uveitis.

Intraocular inflammation/uveitis can be classified in a variety of ways. Some classifications are based on the location of the principal lesion (anterior or posterior), the severity and course (acute, chronic or recurrent), pathology (nongranulomatous versus granulomatous), demography, laterality or associated factors, or according to etiology (bacterial, viral, fungal, parasitic, immunological, systemic, neoplastic disorders simulating uveitis). In the vast majority of cases, the uveitis is thought to be primarily an autoimmune response, probably initiated by a specific etiologic agent, such as bacteria, virus, fungus, protozoa or other infectious agent, or by trauma.

The classic histopathologic approach to uveitis separates it into two groups: 1. Acute inflammation, either suppurative or non-suppurative, and 2. Chronic inflammation, either granulomatous or non-granulomatous. Acute inflammation is generally associated with a polymorphonuclear leukocyte response, while chronic inflammation is associated with a mononuclear cell infiltrate. Acute inflammation of the suppurative type would be characterized by the presence of necrotic and degenerated polymorphonuclear leukocytes.

Chronic inflammation is classified as granulomatous or non-granulomatous disease. Granulomatous disease is further subdivided into three categories: A. Zonal granulomatous inflammation, B. Diffuse granulomatous inflammation, and C. Sarcoidal or discrete type of granulomatous inflammation. This subdivision has been found helpful in identifying specific entities, such as sympathetic ophthalmia, tuberculosis, Herpes zoster infection, phacoanaphylaxis and others.

Zonal granulomatous inflammation exhibits distinct zones of inflammatory response; a central zone of necrosis, surrounded by a zone of neutrophils or epithelioid and multinucleated giant cells and, in turn, this zone is surrounded by lymphocytes, histiocytes, and numerous vessels. It is this necrotic center that a causative agent is most likely to be found; for example, fungi, stained with periodic acid-Schiff or Gomori s methenamine silver or the mycobacterium tuberculosis by acid fast staining.

Rheumatoid sclero-uveitis also falls into this subdivision of zonal granulomatous inflammation. The characteristic lesion, as seen in the sclera, is as described above, including the central scleral necrosis with its mantle of neutrophils, epithelioid and giant cells surrounded by a broad zone of nonspecific chronic inflammation reaction. This can extend to involve the overlying episclera and the underlying choroid and/or ciliary body.

Lens induced uveitis is also an example of the zonal type of granulomatous inflammation/uveitis. A zone of neutrophils, mononuclear cells, some of which are transformed into epithelioid and giant cells surrounds exposed lens fibers. Adjacent iris and ciliary body are inflamed and infiltrated with plasma cells and lymphocytes.

Diffuse granulomatous inflammation is distinguished, as the name implies, by diffuse lymphocytic infiltration with widespread presence of epithelioid cells, which occasionally exhibit focal accumulations or nests. Necrosis is rare, and, when seen, is minimal and inconspicuous. Examples of diffuse granulomatous inflammation involving the uvea include sympathetic ophthalmia and Vogt-Koyanagi-Harada disease.

Sarcoidal granulomatous inflammation is a discrete non-necrotizing granulomatous disease, without a zonal pattern. The granulomata are all about the same size, separated by a small amount of inflammatory cells that are mainly lymphocytes with some plasma cells. Distinctive, but not pathognomonic, inclusions found in the giant cells of sarcoidosis include star shaped, acidophilic asteroid bodies; spherical, basophilic, calcific, frequently laminated Schaumann bodies; and birefringent calcium oxalate crystals.

Intraocular inflammation/uveitis with accompanying conjunctival nodules can prompt conjunctival biopsy. Conjunctival nodule and lacrimal gland biopsy can reveal the noncaseating epithelioid cell granuloma of chronic sarcoidosis. Other etiologic agents, such as coccidioidomycosis, syphilis and tuberculosis, can also be identified on conjunctival biopsy using H & E stains supplemented by Gomori s methenamine silver, Warthin Starry stain (syphilis) and acid fast staining, as well as immunohistochemical staining using antibodies.

An iris biopsy has been found to be helpful in diagnosing several conditions, such as juvenile xanthogranuloma, leukemia, metastatic tumors, tuberculosis and leprosy. These diseases frequently involve the iris, and they can present as either acute or chronic anterior uveitis. In juvenile xanthogranuloma, the iris biopsy is typically diffusely or focally thickened with an infiltrate of large pale staining mononuclear cells, histiocytes, lymphocytes, eosinophils and multinucleated Teuton giant cells.

Posterior uveitis may also present a diagnostic and management problem that can be alleviated by vitrectomy, which may distinguish between idiopathic uveitis, infectious uveitis and a masquerade syndrome, be diagnostic for many etiologic agents, or be diagnostically helpful if certain antibodies are found. For example,

the presence of eosinophils and ELISA testing on vitreous specimens may be helpful in cases of Toxocara nematode infections.

Vitrectomy plays a vital role in the diagnosis of primary intraocular lymphoma, a malignant neoplasm that can involve the retina and vitreous, the central nervous system or visceral organs.

Vitrectomy can be used in the identification of other etiologic agents in intraocular inflammation/uveitis. Some examples include bacterial agents such as Propionibacterium acnes, or fungal agents such as Candida, Cryptococcus or Aspergillus. Aspergillus endophthalmitis may present as a retinitis that mimics toxoplasmosis, and vitreous biopsy can establish the true diagnosis. The septate, narrow, regular and branching hyphal elements are seen clearly with a Gomori methanamine silver or periodic acid-Schiff stain.

In some instances a biopsy of the retina may be necessary to establish the diagnosis, particularly when both eyes are involved and there is great potential for loss of vision, as in the case of acute retinal necrosis. This has been shown to be caused by varicella zoster or a member of the herpesvirus group: herpes simplex, herpes zoster or rarely cytomegalovirus.

In summary, classification of intraocular inflammation/uveitis according to the location of the principal lesion coupled with the discriminating selection of appropriate histopathologic examination (i.e., conjunctival or lacrimal gland biopsy, anterior chamber tap, iris or vitreous biopsy), is one of the best ways to diagnose and manage unusual and challenging uveitis.

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Anterior chamber tap and aqueous humor analysis

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KEY messages

- Differentiation between infectious and non-infectious uveitis is often of crucial value for accurate management of patients with intraocular inflammation.
- Aqueous humor analysis may provide useful information to establish a specific diagnosis of intraocular inflammation in order to confirm or exclude a suspected specific etiology.
- Analysis of aqueous humor yields more relevant information about the local process than those performed in serum.
- Specific analysis, e.g. in suspected mascerade syndromes should be performed in specialized centers.

Background

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

General aspects on anterior chamber puncture in uveitis

Patient selection

An anterior chamber puncture may be considered in case of acute and chronic endophthalmitis, progressive inflammatory eye disease, severe bilateral uveitis and uveitis irresponsive to the previous treatment in order to establish or exclude a specific diagnosis. Patients for anterior chamber puncture are selected mainly for diagnostic purposes.

Timing of diagnostic tap

In general most experts advocate that a suspected intraocular infection has to be

examined in the active state of an inflammatory process in order to proof a specific origin of intraocular inflammation. Several studies have shown that depending on the diagnostic technique that is applied a time frame between 1-6 weeks is critical e.g. for detection of local antibody formation. Little information is available in patients on the time frame of B cell activation. However, from experimental data an onset as early as 3 days has been reported in recurrent disease.

Preparation and anaesthesia

Since the procedure itself is relatively simple and straightforward, there are no major restrictions that apply for an anterior chamber tap. However, since it is an elective intraocular procedure, all precautions have to be taken to minimize any risks. Particular concerns are:

- i.o. infections by entering the eye
- damage to intraocular structures
- trauma to the lens and induction of cataract

In almost all patients topical anaesthesia is appropriate. Lidocain gel or repeated procaine eye drops applied briefly before the procedure are adequate. Concomitant sedatives are not helpful. It is our experience that even in cooperative children anterior chamber tap is a safe procedure. In rare instances, i.e. in uncooperative individuals (e.g. young children, mentally handicapped patients) mask anaesthesia might be preferred.

Technical procedure

Anterior chamber tap is performed as an outpatient procedure. All precautions have to be taken to provide the highest standard of care in this elective procedure. Therefore a diagnostic tap e.g. at the slit lamp is not advised, instead a standard preparation performed as for any intraocular surgery is recommended. After informed consent has been obtained, patients should be prepared with PVP iodine, prepped and draped utilizing sterile technique. After application of one drop of polividone 5%, a speculum retracts the eyelids and a sponge or a little anatomical forceps may be used to stabilize the eye. We are using a 30-gauge needle (bevel up) placed through the clear cornea in the temporal inferior quarter of the eye over the iris stroma to aspirate approx. 100-250 µl of aqueous humor. After puncture, local antibiotics are prophylactically given for 3 days.

Diagnostic procedure

General considerations

Obviously, understanding the underlying pathobiology is a prerequisite for a successful diagnostic strategy. Hence the aqueous humour sample volume is limited

to maximally 200 µl, only two to three tests can be performed. Therefore, a working diagnosis and a diagnostic strategy need to be obtained in advance. As anterior chamber puncture is considered namely in unclear diagnostic situations, this may be the critical point regarding the sensitivity of aqueous humour analysis. Aqueous humour analysis might be considered after serum tests have come back and failed to establish any diagnosis. Moreover, aqueous humour analysis without parallel serum testing is helpful in the detection of a causative agent or process, such as locally restricted infection or malignancy using microbial culture, antigen detection, PCR and cytokine assays. In contrast, the assessment of the humoral immunity with determination of antibody concentration only from aqueous humour without parallel testing of serum cannot be expected to serve any meaningful result. Thus, diagnostic testing of aqueous humor needs to be carefully planned before surgery. Specimen needs to be collected carefully in order to attempt a total volume of aqueous of at least 100-200 µl. As outlined, analysis of the humoral immune response requires an additional blood sample in parallel (2-5 ml). Both samples are portionized according to the minimum volume requirements for the tests to be done and forwarded after personal announcement to the corresponding laboratories.

In patients requiring cytology or culture of intraocular organisms, aqueous is transported at room temperature overnight. Specimen for PCR and antibodies may be refrigerated, depending upon the time until the assay can be performed. Freezing may result in a 10% loss of antibodies and should be restricted to samples which are not worked up within seven to ten days. Coordination with the laboratory prior to analysis is necessary to avoid waste or damage to the specimen.

Indication for anterior chamber puncture

Diagnostic aqueous humor analysis is usually performed in intraocular inflammation with an atypical presentation which threatens visual acuity and does not adequately respond to therapy. The intent is to confirm or exclude an infectious etiology or masquerade syndrome such as intraocular lymphoma (Table 1). For the diagnosis of chronic non-infectious immunologic intraocular inflammation there has so far no assay for aqueous humour tested useful.

Diagnostic techniques

None of the commercially available tests is designed for aqueous humour analysis. This is important to mention since intraocular antibody synthesis is often well below the cut off levels of these tests. This implies that quantitative analysis may be achieved if the sample is analysed besides routine using a higher sensitivity set up for the scheduled assay or if it is individually diluted, usually ten- to hundredfold below the standard dilution factor for testing depending on the volume requirements of the tests.

Progress in molecular biology has allowed novel diagnostic approaches to investigate intraocular infection. A close collaboration with a microbiology department with sufficient expertise to analyse infectious agents in intraocular specimen as well as an immediate transfer of material to a cytopathology department is essential. Besides classical culture techniques, detection of DNA by polymerase chain reaction (PCR), antibody titers and immunoblots are the most frequent applied techniques.

PCR

PCR is a highly sensitive method to accurately detect DNA even from small sample volumes. However, the limitations and possibilities of this technique have to be kept in mind. Possibly the yield is largely dependent on sample processing and the skills of the investigator. The introduction of DNA-based methods have greatly increased the identification rate of a causative organism. The identification of viral DNA and of bacteria after amplification of a common bacterial DNA sequence (16S ribosomal RNA) allows for distinction of the major viral and bacterial causes of severe intraocular inflammation and postoperative endophthalmitis. However, all of these laboratory tests may contribute little if they are not based on clinical grounds. Furthermore, the detection of microorganisms by means of microbiological or molecular techniques, does not necessarily confirm their active contribution. And most importantly, detection of microbial presence may also be attributable to falsely positive test results due to sample contamination. Finally, the negative predictive value of testing is varying widely depending on the target DNA to be detected and the individual laboratory assay performance. Therefore, the information obtained has always to be interpreted in the clinical context considering sensitivity and specificity of the tests in the particular laboratory.

Local antibody formation

Local production of antibodies is confirmed by the Goldmann–Witmer coefficient (GWc), which is the ratio of the local pathogen-specific titer×total systemic antibody titer over the systemic specific×total local antibody titer. An index of over 3 is considered proof of a specific intraocular infection. During primary intraocular infection affecting the posterior segment calculation of the GWc may be the only reliable way of confirming or establishing a specific clinical diagnosis.

Cytology

Generally, information pertained from cytology is of limited value due to the low total cell number even during significant cellular infiltration of the anterior chamber. However, cytopathology may uncover an underlying fungal, mycobacterial or lymphomatous etiology. The major diagnostic challenge lies in the distinction between inflammatory lymphoid infiltrates and intraocular lymphoma in particular when only very few intact cells are present. Nevertheless, cytological determination

of cell surface markers and cytokine levels yield sufficient sensitive results and thus provide valuable information for the diagnostics of intraocular lymphoma.

Postoperative complications

According to published evidence and personal experience, anterior chamber puncture is a sufficiently safe procedure to recommend it if a specific diagnosis needs to be confirmed or excluded. In a retrospective study of 361 patients with uveitis, who underwent a diagnostic anterior chamber paracentesis no severe intra- or postoperative complications were reported. Within a follow-up of at least 6 months no serious side effects such as cataract, keratitis, or endophthalmitis were observed. A small hyphema may occur intra- or early postoperatively in particular in patients with heterochromic iridocyclitis and viral anterior uveitis ("Amsler sign") in 5-7% of cases. Rarely, namely in the case of longer preexisting secondary glaucoma, significant retinal hemorrhage may be observed. Occasionally, minor leakage from the paracentesis might transiently go along with a reduced intraocular pressure. Infectious complications have rarely been observed though these can never be excluded, and clearly any precaution has to be taken to prevent these complications.

Suspected Disorder	Timing of puncture	Preferred method of analysis	Comments	References
HSV-Keratouveitis	Active disease	PCR and AB	Sensitivity of combined analysis nearly 40%	19, 25, 27
Heterochromic cyclitis	Any time ?	AB and PCR	Rubella virus (HSV, CMV)	24
Acute retina necrosis syndrome	Active disease, maximal 48hrs after begin of antiviral therapy	PCR (+AB)	Emergency situation	5, 8, 16, 20, 29
Toxoplasmosis retinochoroiditis	Active disease	AB; PCR in atypical and severe cases	Mainly in atypical clinical presentations	9, 13, 28
CMV Retinitis	Active disease	PCR (+ AB)	Local antibody synthesis might be impaired in HIV+ pts.	6
Mascerade syndrome	Any time	Spin down cytology, analysis of interleukin 2, 6, 10 levels, immunocytochemistry	Analysis in specialized centers	7

AB = Antibody synthesis
PCR = Polymerase chain reaction

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Indocyanine Green Angiography

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Since the introduction of digitalized imaging systems and the use of performing infrared cameras, indocyanine green angiography (ICGA) has been the object of renewed interest because of the good quality and reproducibility of images allowing their systematic analysis. [2,3] A basic introduction on the principles and interpretation of ICGA in inflammatory diseases is indispensable for a comprehensive appraisal of choroiditis going beyond the usual purely descriptive approach.

1. Physicochemical properties of indocyanine green (ICG)

Indocyanine green fluoresces at 830 nm and therefore is giving access to the choroidal vascular structures through the retinal pigment epithelium. The molecular weight difference between ICG (775 daltons) and fluorescein (354 daltons) molecules does not account for the specific angiogram pattern obtained with ICG as compared with fluorescein. Beside the different wavelength at which ICG fluoresces, the crucial difference between these two fluorescing molecules comes from their binding affinity to proteins. [4,5] The ICG molecule is nearly completely protein bound and predominantly so to large sized proteins (lipoproteins) [6] , whereas only about 80% of fluorescein is protein bound and predominantly so to smaller proteins such as albumins. Fluorescein leaks readily from slightly altered retinal vessels with minor damage to the bloodretinal barrier and readily impregnates tissues, whereas only major damage to retinal vessels allows ICG to leak. [7] In the choroid however ICG leaks unimpaired but slowly from the fenestrated choriocapillaris. [8] During recirculation more and more ICG is entrapped in the choroidal tissue as the ICG-protein complex is only slowly reabsorbed into the circulation. Gradual impregnation of the choroid occurs with time causing intermediate and late choroidal background fluorescence. This choroidal impregnation by ICG fluorescence is disturbed by choroidal inflammatory lesions, causing mostly areas of decreased or absent fluorescence and/or increased fluorescence. It is this alteration of the slow choroidal impregnation process that is the main parameter studied in ICGA performed for posterior uveitis.

Summary 1 :

- **The two principal properties of the indocyanine green molecule are fluorescence in the infrared wavelengths and a macromolecular behaviour because it is nearly 100% linked to proteins.**
- **Infrared fluorescence can be detected through the retinal pigment epithelium and gives imaging access to the choroid.**
- **The macromolecular ICG-protein complex egreses from the vascular bed only when capillaries are fenestrated (or when larger vessels are severely inflamed) and so impregnates the choroidal stroma. Absence of ICG fluorescence can mean non perfusion of the choriocapillaris or impaired diffusion of the molecule because of the presence of inflammatory foci.**

2. Standard ICG angiographic protocol for inflammatory diseases

A standard ICGA protocol to analyse choroiditis has been designed. [9] The angioraphic procedure comprises 3 main phases; the early phase up to 2-3 minutes showing superimposed retinal and choroidal large vessels and incipient exudation of the dye through the choriocapillaris into the choroidal stroma. The intermediate phase at about 10 minutes shows maximum choroidal stromal background fluorescence and the late phase at about 28- 32 minutes shows wash-out of the dye from the general circulation with the large choroidal vessels appearing dark against the background stromal fluorescence. [9]

Summary 2 : indocyanine angiography : indication, technique and characteristics for inflammatory diseases of the fundus

- **If choroidal involvement is suspected dual fluorescein and ICG angiography is indicated (allows complete and thorough work-up of inflammatory involvement of all structures and is essential for follow-up of choroidal inflammation)**
- **Use a conventional fundus camera coupled to an image digitalizing system (easier for peripheral imaging) or a scanning laser ophthalmoscopy system.**
- **Use one vial of 25 mgs indocyanine green diluted in 7.5 cc of physiologic saline solution (Cardiogreen®, Akorn, Inc., Buffalo Grove, IL, USA). In case of iodine allergy use iodine-free Infracyanine® (SERB Laboratories, Paris, France)**
- **Angiographic procedure: (1) exclude autofluorescence by taking frames with the highest flash intensity previous to the dye injection; (2) perform early frames of the posterior pole up to 2-3 minutes (early phase); (3) perform posterior pole and 360 degree periphery panoramic frames at 8-12 minutes (intermediate phase); (4) perform fluorescein angiography between**

intermediate and late ICGA phases; (5) perform posterior pole and 360 degree periphery panoramic frames at 28-35 minutes (late phase).

3. Principles for the interpretation of ICGA [9,10]

When analysing ICG in posterior inflammatory disorders crucial differences with fluorescein angiography interpretation have to be born in mind to correctly analyse the images obtained.[10] During initial circulation, ICG is comparable to fluorescein showing the passage through arteriovenous compartments except that it shows superimposed retinal and choroidal circulations. The difference occurs during recirculation time when ICG is progressively leaking out from the fenestrated choriocapillaris, gradually and physiologically impregnating the whole choroidal thickness.
This process can be altered in 2 ways that can be associated in the same disease, either there is a decreased fluorescence or an increased fluorescence.

ICG hypofluorescence (Table 1)

The impregnation of the choroidal space can be absent (<u>hypofluorescence</u>) either (1) by a decrease of the physiological extrusion of the ICG from the choriocapillaris (non perfusion or hypoperfusion) or (2) by the impairment of the filling of the

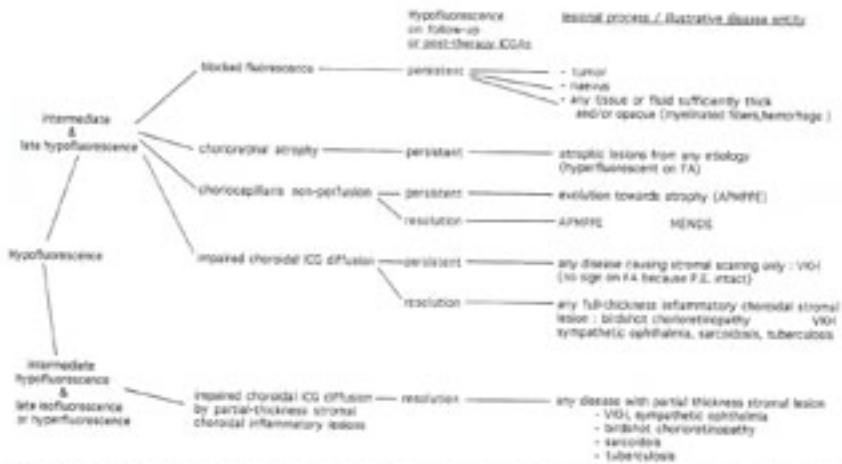

Figure 10. Schematic approach of indocyanine green angiography interpretation to evaluate hypofluorescence. For inflammatory diseases, interpretation of hypofluorescence should be based on intermediate phase frames (12 ± 3 minutes), late phase frames (40 ± 10 minutes), and follow-up and/or post-treatment angiograms.

Table 1.

choroidal tissue by the ICG molecule because of the presence of space-occupying lesions (inflammatory foci). These lesions are hypofluorescent in the intermediate angiographic phase. If they remain hypofluorescent in the late phase this signifies that the inflammatory lesion occupies the whole thickness of the choroidal stroma. When lesions become isofluorescent in the late angiographic phase inflammation causes only partial thickness infiltrates. Therefore, in ICGA performed for inflammatory disorders, the main information is obtained less from the analysis of the early circulatory phase than from the analysis of the altered pattern of the filling of the choroidal space.

ICG hyperfluorescence (Table 2)

Impregnation of the choroidal space can be enhanced (hyperfluorescence) by increased leakage from the larger choroidal vessels. The vessels appear fuzzy in the intermediate time frames and extrusion of the dye from large vessels causes late diffuse hyperfluorescence.
In case of the presence of inflammatory foci in the choroidal stroma, hyperfluorescence is associated with hypofluorescent dark dots due to inflammatory infiltrates..
Hyperfluorescence occurs in three relevant situations, (1) diffuse late phase hyperfluorescence due to leakage from precapillary or larger non fenestrated choroidal vessels, (2) disc hyperfluorescence indicating severe inflammation and (3) hyperfluorescent pinpoints occurring in granulomatous choroidal disease.
In most cases, unlike in fluorescein angiography where most pathologies produce hyperfluorescence, the lesions in ICGA are mostly seen in a negative dark pattern due to impaired physiological choroïdal fluorescence.

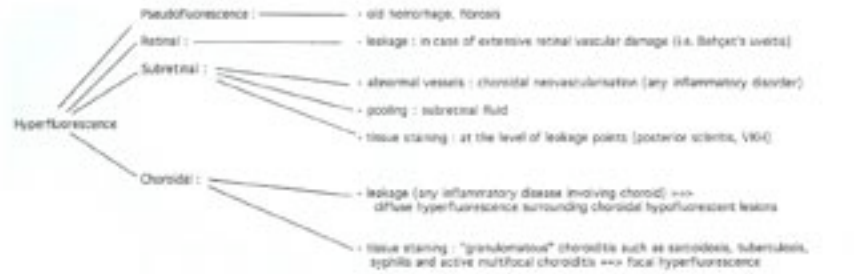

Figure 5. Schematic approach of indocyanine green angiographic interpretation in uveitis: hyperfluorescence. For inflammatory disorders, hyperfluorescence advantageously is classified according to presumed anatomic localization (e.g., retinal vs. choroidal) rather than according to presumed pathogenic mechanism (e.g., staining vs. leakage).

Table 2.

4. Differences between fluorescein and indocyanine green angiography

When analysing ICGA it is of utmost importance to make abstraction in most inflammatory situations of two factors that are important in the interpretation of fluorescein angiograms, namely blockage and window defect. Because infrared fluorescence can be seen through structures that are a screen for visible light, blockage has to be considered only if the interfering structures in front of the choroid are sufficiently thick and/or heavily pigmented. Similarly the notion of window defect does not usually apply for ICGA as the retinal pigment epithelium does mostly not act as a screen as in fluorescein angiography.

5. Clinico-pathologic-angiographic correlations

The pathologic processi at the origin of the ICGA images we see have been verified histopathologically for some of the diseases such as the primary stromal choroiditides Vogt-Koyanagi-Harada disease, sympathetic ophthalmia and birdshot chorioretinopathy, as well as the choroidal lesions of sarcoidosis, while others can still only be hypothesized, needing ICGA-clinico-pathologic correlations.

6. Relevance of ICGA in ocular inflammatory diseases

Indocyanine green angiography showed occult choroidal lesions not shown by fundoscopy and/or fluorescein angiography in 100% of patients with a well-established diagnosis known to involve the choroid and these findings had an essential impact either on diagnosis or management in 12.3% of these cases, stressing the importance of ICGA for the proper management of most inflammatory processi of the back of the eye. [11]

Summary for the clinician: ICGA principles

- **To investigate all superficial fundus structures, the retinal vessels, the retinal pigmentary epithelium (RPE, investigate thanks to the FA principles of blockage and window-effect) and the choriocapillaris in the early angiographic phase, fluorescein angiography is the exam of choice.**
- **ICGA indicated, unavoidable and the exam of choice for the proper investigation of choroidal inflammatory involvement**
- **ICGA hypofluorescence results from 2 mechanisms :**
  (1) choriocapillaris non-perfusion (patchy/geographic disposition; persistent or even increased hypofluorescence on late frames),
  (2) stromal inflammatory infiltration (more regular dots and more even distribution)

- hypofluorescence up to late frames (full-thickness lesion)
- isofluorescence on late frames (partial-thickness lesions)
- usually surrounded by leakage of large choroidal vessels (fuzzy aspect in intermediate phase followed by diffuse choroidal fluorescence in late phase)

- **ICGA hyperfluorescence :**
  (1) in its diffuse form results from increased leakage from larger inflamed choroidal vessels
  (2) when present at the level of disc indicates severe inflammation
  (3) when present in the form of numerous hyperfluorescent pinpoints indicates granulomatous disease
- **FA principle of window effect not applicable for ICGA as infrared fluorescence is perceived through the RPE that is not a screen in ICGA**
- **FA principle of blockage only rarely plays a role in ICGA (unless thick or strongly pigmented screen) in which hypofluorescence mostly caused by choriocapillaris non perfusion or choroidal stromal infiltration**

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Fuch's/Posner/HLA B27

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HLA-B27 related uveitis

HLA-B27 acute anterior uveitis can occur with only ocular involvement, or as part of the seronegative spondyloarthropathies, such as ankylosing spondylitis, reactive arthritis (including Reiter's syndrome), psoriatic arthritis, and inflammatory bowel disease. The prevalence of HLA –B27 in the general population varies geographically; in the western world it is 8–10%, whereas the prevalence of HLA-B27 in patients with AAU is about 50%. Patients with HLA-B27 have a 1-2% lifetime risk of developing uveitis, which increases to 7% for psoriatic arthritis, 3-11% for inflammatory bowel disease, and up to 40% with reactive arthritis or ankylosing spondylitis. Acute anterior uveitis may be the first symptom of a seronegative spondyloarthropathy, preceding the onset of other clinical manifestations.

Clinical Features

HLA-B27 +ve AAU displays a number of characteristic clinical features than can help to differentiate it from HLA-B27 -ve AAU (Table I). There is a high frequency of recurrence with a highly variable interval between attacks, although most usually about 14–25 months. There may also be a decrease in the frequency of attacks with increasing duration of disease. Typical cases are unilateral but may "flip-flop" to the contralateral eye with subsequent attacks (unilateral alternating). Inflammation is usually non-granulomatous and if severe can cause a plasmoid aqueous with a fibrin clot or a hypopyon. Differential diagnosis of fibrin in the anterior chamber includes diabetes mellitus, and Behçet's disease may also present with a hypopyon.

A minority of cases may involve the posterior segment secondarily, leading to vision threatening complications such as cystoid macular edema, vitreitis, retinal vasculitis, papillitis, or pars planitis. Occasionally, the inflammation may recur with a painless, white eye and loss of central vision rather than a red, painful eye with photophobia and slightly blurred vision. Examination reveals little or no cellular activity in the anterior chamber but the presence of cystoid macular oedema, presumably secondary to blood retinal barrier breakdown. Periocular injection of corticosteroid is highly effective in these eyes.

HLA-B27 subtypes

HLA-B27 consists of 24 subtypes, encoded by 26 different alleles. These subtypes vary by ethnic/racial origin, with some more associated with risk of AAU than others. The subtypes HLA-B*2705, B*2702 (more common in Caucasoids), and B*2704 (predominant in Asians) are associated with AAU, whereas B*2706 (more common in Asians) and B*2709 (mainly restricted to Sardinians) are weakly associated or not associated. Non-HLA genes within the MHC have also been studied for their possible role in the predisposition to AAU and other spondyloarthropathies. In particular, a significantly higher frequency of the MHC class I chain-related gene A (MICA) A4 allele has been found in AAU Caucasoid patients than in ethnically matched controls. MICA A4 was found to be in strong linkage disequilibrium with HLA-B27, however the A4 allele was also found at significantly higher frequency in the HLA-B27 -ve AAU patients compared to the ethnically matched HLA-B27-negative controls, suggesting that the MICA gene itself or other nearby gene(s), closely linked to the MICA A4 allele, may be involved in the development of AAU. Recently, genome-wide scanning has identified a genetic region for AAU. Even though ankylosing spondylitis was highly prevalent in this cohort of families, a locus at chromosome 9p21-9p24 was identified that uniquely associated with AAU.

Apart from these genetic associations, environmental factors may also play a role. There is extensive evidence implicating bacterial infection as a "trigger" for HLA-B27 AAU. The organisms implicated include Chlamydia trachomatis, Klebsiella, Yersinia, Shigella, and Salmonella species, and Campylobacter jejuni. Nevertheless, much of the evidence is indirect and involved the detection of humoral and cellular immune responses to various bacteria.

Table I: Clinical Features of HLA-B27 positive compared to HLA-B27 negative anterior uveitis

Clinical Features	HLA-B27 positive Anterior Uveitis	HLA-B27 negative Anterior Uveitis
Age at onset (years)	32-35	39-48
Gender	Male preponderance 1.5-2.5:1	1:1
Eye involvement	Unilateral 48-59% Unilateral alternating 29-36%	Bilateral 21-64%
Pattern of uveitis	Acute in 80-87%	Chronic in 43-61%
Recurrence	Frequent	Uncommon
Keratic precipitate (KP)	Mutton fat KP in 0-3%	Mutton fat KP in 17-46%
Fibrin in anterior chamber	25-56%	0-10%
Hypopyon	12-15%	0-2%
Associated systemic disease	48-84%	1-13%
Family history	Yes	No
Posterior synechiae	40.4%	18.7%
Cataract	12.9%	13.6%
Ocular hypertension	11.4%	11.4%
Glaucoma	4.4%	6.6%
Cystoid macular edema	11.7%	1.0%

Posner-Schlossman syndrome (glaucomatocyclitic crisis)

Glaucomatocyclitic crisis is caused by an inflammatory process of the trabecular meshwork, causing a decrease in aqueous outflow, resulting in an associated ocular hypertension. There is rarely any pain and the eye is white. Visual acuity may be reduced if there is corneal epithelial oedema. Slit-lamp examination typically reveals only an occasional small non-pigmented keratic precipitate on the corneal endothelium with a mild anterior uveitis (+0.5 to– +1.0 cells in the anterior chamber). The intraocular pressure is increased (30 to 70 mm Hg), despite an open drainage angle. Therapy is aimed at treating the trabeculitis with topical corticosteroid and controlling the increased intraocular pressure with the use of topical IOP lowering agents. Occasionally an oral carbonic anhydrase inhibitor is required. Complications related to prolonged and recurrent attacks of increased intraocular pressure can result in glaucomatous optic neuropathy and corresponding visual field defect. Although this condition is thought to be idiopathic, herpes viruses (HSV and CMV) have been implicated as a possible cause. A significant number of patients glaucoma develop over time, and they need to have their optic disc appearance and visual fields carefully monitored.

Fuchs' Heterochromic Cyclitis (FHC)
FHC is a painless, low grade, chronic uveitis of unknown aetiology. Ernst Fuchs made the first comprehensive clinical description in 1906.

Epidemiology
FHC comprises about 5% of all uveitis entities and most patients present between 20-50 years although a number are older children. There is an equal sex distribution and the condition is almost invariably unilateral (>90%).

Clinical Features

Symptoms
Patients usually present with floaters as a result of vitreous opacification or reduced vision due to cataract. There is no pain or redness.

Signs
A white eye:
Cornea
- stellate, filamentary keratic precipitates (KPs) scattered all over the corneal endothelium, pigmented KPs rarely seen.

Iris
- heterochromia may range from subtle changes around the pupillary zone to widespread iris atrophy
- usually the colour of the affected iris becomes lighter (more blue)
- colour changes are more easily seen in daylight rather than at the slit lamp
- a smooth, pale surface with blunting of crypts, a dull stroma and loss of crispness of iris architecture
- nodules on the pupil margin (Koeppe) or on the iris surface in the pupillary zone are found in up to one third of patients
- iris crystals
- posterior synechiae do not form.

Anterior Chamber (AC)
- there is mild AC activity, usually 1+ to 2+ cells.

Intraocular Pressure (IOP)
- fine, radial new vessels may be seen in the angle on gonioscopy
- secondary glaucoma can occur in up to 25% of patients – most of these patients present with raised IOP.

Lens
- posterior subcapsular cataract develops in at least 80% of eyes.

Vitreous
- some degree of vitreous opacification, in the form of veils and cells, is found in

most patients and sometimes may be so severe as to limit the fundal view.

Retina

- small, punched out, pigmented, peripheral chorioretinal scars are seen in about 7% of eyes. Cystoid macular oedema is not a complication.

Investigations

FHC is a clinical diagnosis and unless the diagnosis is in doubt patients do not require investigation.

Medical Treatment

- usually nil as the inflammation is mild and topical steroids appear to have little effect
- in a few patients large numbers of KPs may reduce vision by obstructing the visual axis and a short course of topical steroid can be prescribed
- secondary glaucoma may be refractory to topical therapy and surgery may be often required.

Surgical Treatment

Cataract

- FHC has the best visual outcome from cataract surgery than any other type of uveitis; 90% should get a return of vision to at least the 6/9 (20/30) level
- it is unnecessary to cover the patient with systemic steroid during the operative period
- phakoemulsification is performed and a posterior chamber intraocular lens can safely be implanted (usually an acrylic lens)
- a filiform haemorrhage (Amsler's sign) from the angle, starting opposite from the site of entry into the eye, is a characteristic finding
- a flare-up of inflammatory activity may be seen in patients in the immediate post-operative period and under these conditions posterior synechiae can form.

Glaucoma

- trabeculectomy (± an antimetabolite, such as 5-fluorouracil or mitomycin C) appears to be successful in controlling the glaucoma
- occasionally a tube may be required.

Vitrectomy

- visually disabling vitreous opacities will benefit from vitrectomy. In some cases it is undertaken in combination with cataract surgery.

Aetiology
The cause of FHC has remained an enigma since the condition was first described a number of theories have been put forward and these include:

Sympathetic
As iris hypochromia can result from a lesion of the sympathetic nervous system, a neurogenic cause for FHC has been postulated. Cases of FHC have been reported in association with conditions due to a sympathetic defect

- Horner's syndrome
- status dysraphicus (unilateral syndrome of dysmorphism and asymmetry)
- Parry Romberg syndrome (progressive facial hemiatrophy).

Despite this the evidence for FHC resulting from a sympathetic defect remains weak.

Genetic
There are reports of more than one family member having FHC, including sets of monozygotic twins. However, there are no strong HLA associations so a genetic basis for FHC remains unlikely.

Infective
Some authors believe that an association exists between FHC and ocular toxoplasmosis because of the presence of 'toxoplasma-like' scars in the fundi of FHC patients, and reports of a few cases of active and inactive toxoplasma retinochoroiditis in association with the typical features of FHC. However, this association cannot be substantiated by laboratory tests for toxoplasmosis

- rubella
- (herpes simplex type 1)
- (toxocara)

Vascular

- the presence of vascular abnormalities in the form of new vessels in the angle
- leakage from iris vessels with areas of ischaemia associated with neovascularisation as seen on iris fluorescein angiography.

Although an immune complex vasculitis has been suspected there is no good evidence to support this.

Immunological
This is the most interesting theory as large numbers of immunological aberrations have been identified in the serum and aqueous humour of FHC patients:

- intraocular IgG production with oligoclonal IgG bands
- raised levels of circulating sIL-2 receptors

- antiendothelial cell antibodies and various adhesion molecules in the circulation
- Th1-like cytokine profile in the aqueous.

Despite these abnormalities patients are free of the systemic manifestations of immune mediated disease.

Conclusion

FHC may not be a specific clinical entity as it has been seen in association with:

- Coats' disease
- retinitis pigmentosa
- sarcoidosis
- toxoplasmosis
- toxocariasis

It may be a secondary response to a variety of different aetiological agents, with the triggering stimulus being possibly immunological, infectious, or a combination of both.

Key Points

- the diagnosis may not be immediately obvious at initial presentation and other features may develop over many years – patients may have unnecessary treatment
- signs of bilateral inflammation should promote the search for an alternative diagnosis, such as intermediate uveitis
- the KPs may be absent if the patient is being treated with topical steroids which may make the diagnosis difficult
- the presence of iris nodules should alert one to think of this condition
- it is more common for patients to present with raised intraocular pressure than to develop it at subsequent follow-up
- vitreous opacification should not divert the ophthalmologist from the diagnosis.

JCA + paediatric uveitis

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AIDS today (AIDS, CMV)

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Herpetic ocular disease

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

Epidemiology

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

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

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

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

Clinical characteristics

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

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

Anterior uveitis

1) Herpes simplex anterior uveitis

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

Symptoms and signs

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

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

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

2) Herpes zoster anterior uveitis

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

Symptoms and signs

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

3) Cytomegalovirus anterior uveitis

Recently iridocyclitis due to CMV, without CMV retinitis has been reported in immunocompetent patients (4, 5). This is a recurrent, and in some cases chronic, unilateral iridocyclitis with symptoms and signs similar to those of HSV anterior uveitis. Sectoral iris atrophy and ocular hypertension or glaucoma are common findings. In one report the patient's ages ranged from 30 to 80, with a median age of 50 years. PCR of aqueous confirms the diagnosis. CMV iridocyclitis should be considered, along with HSV and VZV inflammation in every case of recurrent, unilateral anterior uveitis.

Diagnosis of herpetic anterior uveitis

The diagnosis is usually clinical, and is based on the history and signs on ophthalmic examination. Anterior chamber paracentesis to detect locally produced anti-HSV, anti-VZV, or anti-CMV antibodies (Goldmann-Witmer coefficient), or viral DNA (PCR) confirm the diagnosis in equivocal cases. The differential diagnosis includes Fuch's heterochromic cyclitis, Posner-Schlossman syndrome, and other herpetic anterior uveitis.

Treatment

All forms of herpetic anterior uveitis respond well to topical steroid therapy. Cycloplegics reduce the risk of posterior synecheae formation, and topical anti-glaucoma agents are given for hypertony. The major problem is recurrence of inflammation, which can lead to major ocular complications. Oral acyclovir (800mg/day) has been shown to reduce the recurrence rate of herpetic corneal stromal disease, with a prophylactic effect for as long as the antiviral regimen continues.(6). Smaller studies (7) and clinical experience suggest that prophylactic oral acyclovir reduces the rate and severity of anterior uveitis recurrence. Acyclovir is effective for HSV iridocyclitis, and valacyclovir and famcyclovir have been used for VZV iridocyclitis. Gancyclovir (4), valgancyclovir (5), and valacyclovir (8) have been reported to be effective in CMV anterior uveitis.

Complications

Secondary glaucoma and posterior subcapsular cataract are the most common complications of herpetic anterior uveitis.

Necrotizing herpetic retinopathies

Necrotizing herpetic retinopathy is a term used to describe a spectrum of posterior segment disease entities caused by the herpes viruses. They are all characterized by

necrotizing retinitis or chorioretinitis, but each presents distinct clinical characteristics. They are: 1) Acute retinal necrosis (ARN)
2) Progressive outer retinal necrosis (PORN)
3) Cytomegalovirus retinitis (CMVR)

1) Acute Retinal Necrosis (ARN)

ARN can occur in immunocompetent individuals, as well as in immunocompromized patients. It is caused by HSV-1, HSV-2, less commonly VZV and rarely CMV. ARN is a bimodal disease with two peak ages of incidence: 20 years (usually HSV), and 50 years (most often VZV). It is unilateral in approximately 70% of cases. Bilateral ARN (BARN) is more common in association with immunodeficiency.

Symptoms and signs

ARN begins with an anterior uveitis. Patients complain of redness, ocular pain, and blurring of vision. Fine or mutton-fat keratic precipitates and elevated intraocular pressure are common findings at this stage. Within 1 to 2 weeks discreet yellow-white deep retinal lesions appear, usually between the mid-retinal periphery and ora serrata. As the inflammation progresses, a dense vitritis develops, and the necrotizing retinal lesions coalesce and spread quickly peripherally, posteriorly and circumferentially. Occlusive arteritis and perivasculitis are characteristic features, and are accompanied by optic nerve head swelling and choroidal thickening. Retinitis regresses starting from the outer peripheral borders, leaving retinal atrophy with pigment epithelial changes ("salt and pepper pigmentation"). The atrophic retina is extremely thin and friable, forming breaks and holes at the border between healthy and atrophic retina. Combined with the cellular infiltration of the vitreous, this leads to tractional/rhegmatogenous retinal detachments in approximately 75% of cases.

Diagnosis

The diagnosis of ARN is mainly clinical, based on the characteristic triad of findings: confluent peripheral necrotizing retinitis, acute retinal arteritis and vitritis. Immunofluorescence staining with virus-specific antibodies, in situ hybridization of vitreous, or PCR of aqueous or vitreous confirms the diagnosis and determines the specific causative virus.

The differential diagnosis includes Toxoplasmic retinitis, CMV retinitis, and intraocular lymphoma.

Treatment

Treatment should be initiated as soon as possible. Intravenous acyclovir (5-10 mg/kg/day) is given until clinical improvement, followed by oral acyclovir, valacyclovir or famcyclovir, for HSV and VZV ARN. Gancyclovir or valgancyclovir can be utilized for ARN caused by CMV. Oral steroids are added 1 to 2 days following initiation of antiviral treatment. Prophylactic laser can be helpful in preventing retinal detachment. Long-term prophylaxis with oral anti-virals is necessary to prevent recurrence.

2) Progressive outer retinal necrosis (PORN).

PORN is the rarest of the necrotizing herpetic retinopathies, and the most devastating.

It occurs almost exclusively in patients with AIDS and severe immunodeficiency (CD4+ T lymphocytes <50/mm3). It is caused by VZV, and a history of antecedent cutaneous zoster is often present. PORN is more commonly unilateral on presentation, but the fellow eye is often affected during the course of the disease.

Initially multifocal discreet, deep retinal necrotic lesions are present. There is minimal or no anterior chamber and vitreous inflammation, and minimal vasculitis. Perivenular lucency creates the characteristic "cracked mud" appearance of the fundus. The retinitis progresses extremely rapidly, leaving retinal atrophy in its wake, and leading often to total retinal detachment.

Diagnosis

The diagnosis is based on the clinical history of severe immunodeficiency, and the characteristic clinical picture and course of the disease. A high index of suspicion is necessary in order to diagnose the condition and initiate treatment as soon as possible.

Treatment

Treatment should be prompt and aggressive. Ganciclovir and foscarnet, alone or in combination have been used, intravenously, and intravitreally. Valgancyclovir has also been reported to be effective. Induction therapy is followed by maintenance therapy once the retinitis becomes inactive. Concurrently HAART must be initiated, to improve the immune function. Maintenance therapy must continue indefinitely, or until there is substantiated improvement in immune function (HAART-induced immune reconstitution.)

3)Cytomegalovirus retinitis

CMV retinitis is an opportunistic infection that develops only in patients with severe immunodeficiency due to AIDS, malignancies or organ transplantation. It is the most common opportunistic infection in patients with AIDS (9), and occurs usually when the CD4 T lymphocyte count is below 50 to 100/mm3. With the introduction of highly active antiretroviral therapy (HAART) there has been a 75% reduction in the number of new cases of CMV retinitis (10).

Symptoms and signs

Presenting symptoms vary depending on the location of retinal lesions. Patients may complain of floaters and/or vision decrease or may be entirely asymptomatic. For this reason it is crucial to monitor all patients with known immunodeficiency, particularly if the CD4 count drops below 100/mm3.

The eye is usually white and quiet, with minimal or no inflammation in the anterior chamber and vitreous, due to the severe immunodeficiency. Retinitis may present posteriorly, usually adjacent to retinal vessels, as one or more areas of dense white

infiltrate with retinal hemorrhage (hemorrhagic necrotizing retinitis), which has been described as "pizza pie" appearance. More commonly retinitis presents in the periphery, has a granular appearance, with less retinal hemorrhage. Progression is relatively slow and occurs usually in a contiguous fashion, but skip lesions can also occur. Thin atrophic retina with mottled pigmentation is left behind the advancing border of active retinitis, and atrophic holes often form at the junction between healthy and atrophic retina, resulting in retinal detachment. Vision loss is due to direct involvement of the posterior pole, optic nerve, or secondary to retinal detachment.

Diagnosis

The diagnosis is clinical. The history of severe immunodeficiency, in association with slowly progressive hemorrhagic or granular necrotizing retinitis with minimal inflammation is highly suggestive of CMVR. The differential diagnosis includes ARN, toxoplasmic retinitis and syphilis.

Treatment

Treatment must be aimed at: 1) Combating CMV in the eye with local or systemic anti-CMV medications and 2) improving the patient's immune status with combination antiretrovirals, including protease inhibitors (HAART). Anti-CMV agents include gancyclovir (I.V and in the form of the gancyclovir intraocular device), foscarnet (I.V, intravitreally), cidofovir (I.V, intravitreally), fomivirsen (intraocular implant), and oral valgancyclovir.

Induction therapy is followed by maintenance therapy once the retinitis becomes inactive. The patient is monitored closely for progression of retinitis, immune status, and associated extraocular CMV disease. In the pre-HAART era maintenance therapy was continued for life, and reinduction was often necessary if retinitis progressed. HAART-induced immune reconstitution (CD4> 100.mm3) has allowed the discontinuation of maintenance therapy, without reactivation of retinitis (11).

Immune recovery uveitis

Patients with AIDS and inactive CMV retinitis who respond to HAART with improvement in immune function may develop intraocular inflammation termed immune recovery uveitis (IRU)(12). Clinical characteristics of IRU include anterior chamber inflammation, vitritis, papillitis, cystoid macular edema and epiretinal membrane formation. IRU may result in complications including posterior synecheae formation, secondary glaucoma, retinal neovascularization, and vitreo-macular traction syndrome. (13).

Local corticosteroid treatment and anti-CMV agents have been utilized to treat IRU, with varied success. IRU has also been reported in iatrogenically immunosupressed patients with inactive CMV retinitis and improvement in immune function (14).

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Scleritis

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Toxoplasmosis and parasitic infections

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Tb and syphilis

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Lyme disease and other zoonotic diseases

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Lyme disease

Lyme disease is a spirochetal infection transmitted by an arthropod vector. The disease takes its name from the town of Lyme (Connecticut) where in 1975 an outbreak of chronic arthritis occurred. In 1982 the infectious agent was identified as a spirochete and named Borrelia burgdorferi. Lyme disease has a worldwide distribution and endemic area are located in North America, northern Europe and northern Asia.
The disease has 3 typical phases.
Stage 1. It begins days to weeks after the thick bite and it is characterized by spirochetemia. In this stage appear the pathognomonic rash, the erythema migrans, starting at the thick bite. This lesion is 5 cm wide with a central area of clearing and a typical annular erythematous margin. It may be accompanied by fever, flu-like symptoms and arthralgia. In some cases there is not a clear history of tick bite or rash
Stage 2. Dissemination of the spirochete. It may occur even months after the tick bite and represents the spread of the spirochete to different organs, such as skin, heart, joints and central and peripheral nervous system. This stage is characterized by the neurological involvement (meningoencephalitis, Bell's palsy, cranial and peripheral neuropathy). Cardiac involvement and arthritis are also typical of this stage, along with the appearance and disappearance of the skin lesions.
Stage 3. It may starts even months to years after the thick bite and after a disease free period. This stage may occur also after antibiotic therapy has been administered in the early phase of the disease and its typical manifestation is constituted by a chronic relapsing arthritis. Acrodermatitis chronica atrophicans is the most typical skin lesion of this stage, while the neurological involvement comprises of encephalopathy, demyelination and dementia

Ocular manifestations
Ocular lesions can occur in all the stages of the disease. The most frequent ocular lesion is conjunctivitis, being observed in nearly 10 % of the cases. The conjunctivitis is self-limited and characterized by the usual signs and symptoms. Neurophthalmologic lesions are more frequently encountered in stage 2 of the disease, concomitantly with central nervous system involvement. Diplopia, optic neuritis, papilledema are the most typical ocular lesions detected in this stage. An intraocular inflammation,

presenting usually as vitreitis or intermediate uveitis, with or without a chorioretinal lesions and retinal vasculitis, is typical of the last phase of the disease. In endemic areas Lyme uveitis may account for up to 4% of uveitis seen in university clinic. Occasionally stromal keratitis, episcleritis, symblepharon, orbital myositis and posterior scleritis have been also observed in stage 3.

Diagnosis
The definite diagnosis of Lyme disease is made with a culture of Borrelia burgdorferi. The spirochete may be isolated from skin lesion, in peripheral blood and in cerebrospinal fluid but usually only in the early phase of the disease. Later it is possible to make the diagnosis with PCR. The systemic lesions, quite typical if a thick bite is present in the history, may suggest the diagnosis which has to be confirmed at least by the positivity of serum specific antibodies. It is of note that these antibodies may be not detected in the early phase of the disease, and that the presence of serum antibodies, although highly sensitive for Borrelia burgdorferi are not specific and may cross-react with other spirochetes.
Two main categories of ocular lesions have to be differentiated from Lyme disease, infectious and non infectious disorders. Among the first it is important to exclude syphilis, tuberculosis, viral keratitis, infectious arthritis, mononucleosis, mumps and viral meningoencephalitis, while the non-infectious disease resembling Lyme disease are sarcoid, collagenopathy and multiple sclerosis

Treatment
The mainstay of therapy for Lyme disease is antibiotic. They have to be administered as early as possible in order to avoid the progression of the disease, which can be eventually occur even after a specific therapy. Doxycicline (200 mg/day) or amoxicilline (1.5 g/day) should be given for 14 to 21 days, while the ocular and central nervous system lesions respond well to ceftriaxone 2 gr/day i.v, or cefotaxime 6 gr/day for 14 to 21 days. The use of steroid is controversial and no prospective trials have been addressed to ascertain whether it can lower the inflammatory response and it is non responsible for the frequently encountered chronic progression of the disease. Topical steroids have been also used to treat conjunctivitis, keratitis and episcleritis, but also these lesions may relapse during time.

Leptospirosis

Leptospirosis is one of the most common zoonotic infection. It is caused by Leptospira interrogans spirochete. Most commonly encountered in tropical and subtropical region, the natural hosts are rodents dogs, pigs, and cattles, which may transmit the disease to humans through urine, blood and infected water. The spirochete enter

human body through mucous membranes or skin abrasions.
The spectrum of human spirochetosis is wide, ranging from subclinical infection to fatal syndrome (Weil's syndrome).
Two phases of the disease might be observed:
First phase (spirochetemic phase). This phase usually lasts from 2-3 days to 7-10 days and may be characterized by the onset of fever, headache, fatigue and myalgia. Frequently accompanied by abdominal pain, nausea, vomiting and diarrhea. In this phase it is possible to find the spirochetes in blood, cerebrospinal fluid, kidney and other organs. The spirochetemic phase is followed by a **second phase (spirocheturic one, immune phase),** usually after a quiescent period. This occur as a results of immune response to the infection, although also in this phase is it possible to find live leptospira in kidney and eye. This second phase may develop as anicteric leptospiros (90% of the cases) or icteric leptospirosis (10%) Most patients with anicteric leptospirosis have a mild, self-limited disease that usually resolves without sequelae. The immune phase is usually charcterized by the onset of meningitis, or other CNS involvement like encephalitis, cranial nerve palsies, peripheral neuropathy and leptospiruria. Fever may be present and uveitis usually occur during this period. In Weil's syndrome, the catastrophic evolution of a leptopsira infection, multisystem haemorrhages, renal failure, jaundice and cardiac shock occur.

Ocular manifestations
Ocular involvement may be constituted either by conjuctival hyperemia and haemorrhages, which usually are self-limited, presenting without discomfort, lacrimation or discharge and underreported in these patients, or by a usually bilateral uveitis (2-10% of patients with leptospirosis). Uveitis may be observed either early in the course of the disease or years after its onset. Two different types of uveitis have been described in patients with leptospirosis, neither of them with pathognomonic features. One, less frequent at least in Brazil and India, countries with large endemic area of leptospirosis, is typically an acute anterior uveitis, the other is characterized by a posterior involvement which may appear as vitreitis, choroiditis, papillitis or panuveitis with or without hypopion and retinal vasculitis. Cataract may be present in 10% of the patients, and typically oh this infection it has been reported a spontaneous absorption in 18.5% of the cases. The clinical presentation of this infectious disease may vary according to the virulence of the infective organism and the genotype of the host, which may be implicated in the strength of the immune response. Nevertheless in spite of the higher frequency of a posterior and diffuse uveitis, the final prognosis of leptospiral uveitis is fairly good, with a relative low incidence of macular edema and epiretinal membrane formation.

Diagnosis

Diagnosis of leptospirosis can be made either by isolation of the organism, or its DNA, from blood or cerebrospinal fluid, mostly in spirochetemic phase, or by demonstration of rise in specific antiobodies in serum with ELISA. It is of note that 28% of aqueous humor PCR-positive leptospiral uveitis patients did not demonstrate serum antileptospiral antibodies, and this may happen because uveitis is usually observed months or years after the acute illness and the seroconversion.

Nevertheless, as indicated above, uveitis observed in leptospiral infection has no pathognomonic signs. So it is important to consider for differential diagnosis, after collecting a good patient history that may revealed some important risk factors for leptospiral infection, such as living or travelling in endemic areas and low socio-economic status; HLAB27-associated uveitis for anterior uveitis (usually with less vitreal involvement and vasculitis); intermediate uveitis (no anterior chamber significant inflammation and a higher rate of cystoid macula edema); Behçet's disease (typical extraocular symptoms); TB uveitis (PPD positive, chest XRay positive, usually granulomatous uveitis)

Treatment

The treatments of choice for leptospirosis should be either penicillin (1.5M/U or ampicillin 500-1000mg 6 hourly for 10 days) or doxycicline 100 mg twice daily for 10 to 14 days. The therapy should be initiated within 4 days from the infection and some controversies exist on the use of antibiotic therapy in the later stages of the disease. Nevertheless it has been demonstrated that leptospira may survive for months in infected organs, including the eye, so it may be useful to administer an antibiotic treatment even months after the acute phase of the disease. To control the inflammatory reaction a corticosteroid therapy may also be useful. It may be administered either topically in combination with mydriatics and cycloplegics, in order to control the anterior chamber inflammation, or systemically, at least two days after starting specific antibiotic treatment, to reduce the inflammatory reaction of the posterior segment of the eye.

Brucellosis

Brucellosis is caused by a small gram-negative coccobacillus of which many biotypes have been identified: brucella melitensis, brucella abortus, brucella suis, brucella neotomae, brucella ovis, brucella canis a brucella maris. Each species may have one or more hosts, the principal being sheep, goats, camels, cattle, rats, dogs. Brucella abortus is the most common biotypes in animals, whereas human may be infected mostly by brucella abortus, suis, canis and melitensis. Human disease may occur after consumption of contaminated meat, unpasteurized milk or cheese or through

occupational contact with infected animals and their products. Transmission may occur through altered skin or mucous membranes or aerosolization.

Systemic disease

Brucellosis may involve any organ system with non specific signs and symptoms. It may be divided into subclinical disease, acute or subacute illness, localized disease and complications, relapsing infection and chronic disease

Subclinical disease

The incubation period usually is ranging from 1 week to many months. Subclinical disease is usually diagnosed serologically among high-risk individuals and appears with a flu-like syndrome

The acute and subacute disease starts with fever with classic peak in the afternoon, drenching sweats, chills and weakness, and may be associated with malaise, headache, weight loss, myalgia, arthralgias.

Localized disease may be encountered in any organ, more commonly in CNS, heart, lung, hepatobiliary system, skin. Fourty per cent of the cases develop osteoarticular involvement, mainly sacroileitis and arthritis. Abnormal liver function is quite frequent, with a possible formation of noncaseating epitheliod granulomata. Pulmonary, genitourinary, CNS, heart, skin and renal involvement are possible but rare

Relapsing infection is observed in up to 10% of the patients weeks to months after antibiotic treatment due to the intracellular location of the organism and to an incomplete antibiotic therapy.

Chronic disease

If the disease persist for more than 1 year after onset, the chronic phase may be diagnosed Inadequate antibiotic treatment of sequestered organism are the cause of chronic disease which is characterized by different signs of infection or by fatigue, malaise and depression. These symptoms may also occur for a psyconeurosis and the differential diagnosis is quite difficult.

Ocular manifestations

Ocular involvement in brucellosis is quite rare, ranging around 2-26% of the affected persons. The most common ocular lesions are uveitis, usually unilateral, presenting as anterior uveitis, granulomatous or non granulomatous, chorioretinitis or diffuse uveitis. In the acute phase of the disease an endophthalmitis with hypopion may also occur. The most frequent posterior involvement is represented by multifocal choroiditis, presenting as a geographic pattern or associated with nodular exudates with surrounding retinal edema. Papilledema, optic neuritis, arachnoiditis, cranial nerve palsy may be also expression of the dissemination of neurologic brucellosis; retinal vasculitis, scleritis and keratitis have been also described during this infection. Episcleritis and dacryoadenitis may also be diagnosed.

Diagnosis

The diagnosis is made upon isolation and cultures of the organism from the blood, bone marrow or other tissues. A presumptive diagnosis is suggested by elevated or rising titers of specific anti-Brucella antibodies, and should be kept in mind in presence of any patient with uveitis with occupational exposure, history of travel in endemic areas or ingestion of unpasteurized milk or dairy products..

Signs and symptoms of uveitis are quite unspecific in brucellosis and therefore a huge number of uveitic entities should be kept in mind in order to make a differential diagnosis. As for all the uveitis the great mimick of TB and syphilis, Lyme disease (eritema migrans and thick bite), outer retinal toxoplasmosis, diffuse unilateral neuroretinitis (no or little vitreous involvement) viral retinitis (mostly retinal involvement, haemorrhages), sarcoidosis (serologic tests, multifocal choroiditis and panuveitis, absence of occupational or other risk factors).

Treatment

Combination therapy is usually required to avoid the rate of relapse of monotherapy which usually ranges from 10-40%. Although for many years the combination of tetracycline 2 g/day orally for 6 weeks plus streptomycin 1 g/day intramuscularly for 3 weeks has been widely used, the current recommendation of WHO is doxycicline 200 mg/day plus rifampin 600-900 mg/day for 6 week. Fluoroquinolones (ofloxacin 400 mg/day) may also be associated with rifampin with good results, while the treatment of CNS involvement and of endocarditis are usually do with the same drugs for prolonged period (6-9 months). A useful alternatives in such cases might be the association of ceftriaxone and rifampicin. Therapy for the ocular involvement will follow the indications for CNS lesions, considering that drugs crossing the blood-cerebral barrier are also able to cross the blood-ocular barrier. In addition with antibiotic therapy, as for the other zoonoses, a corticosteroids anti-inflammatory treatment is advisable under antibiotic umbrella, to decrease the inflammation in anterior and posterior chamber and to avoid or reduce the possible vision-threatening complications such as macular edema and optic nerve atrophy

Rickettsioses

Rickettsiae are gram negative, obligate intracellular coccobacilli. They are classified into three major categories: the spotted fever group, including Rocky Mountain, Mediterranean, African and Oriental fever, which are usually transmitted by a thick bite; the thypus group (epidemic thypus, endemic thypus and scrub thypus) which are usually transmitted by feces; the other disease group, such as Q fever which may be transmitted either by tick bite or aerosolization. Human infection therefore can follow three mechanisms: 1) direct access the blood stream from skin (tick bite); 2)

the organisms can contaminate a person who scratches a bite, contaminating the wound with infected feces; 3) aerosolization of contaminated products of infected animals. The target cells are the endothelial cells of the blood vessels and their muscle cells. Rickettsiae proliferate intracellularly producing a diffuse damage of small arteries, veins and capillaries resulting in disseminated vasculitis.

Systemic signs and symptoms
The initial clinical presentation is constituted by fever, myalgia and headache. A tache noire develops at the site of the thick bite. Gastrointestinal involvement with nausea, vomiting, and abdominal tenderness is frequent, along with neurologic manifestations (focal deficit to severe neuropsychiatric syndrome). The maculopapular rash, starting at writs and ankles and typically involving the palms and soles, may be present at the time of presentation or in the following days Any organ may be affected, depending also from the different etiologic agent.

Ocular manifestations
Conjunctivits and conjunctival haemorrhages are the most frequent ocular lesions observed in Rickettsioses. Rare reports exist on a corneal involvement and some on a mild to moderate anterior non granulomatous uveitis which usually respond well to topical corticosteroid therapy combined with systemic antibiotic treatment. Posterior segment involvement is very frequent in Rickettioses (up to 85% of the patients in acute stage), although it may be asymptomatic in more than 50% of the cases. Vitreitis, retinal vasculitis, optic nerve edema, retinal haemorrhages, cotton-wool spots, white retinal lesions, macular edema and macular star, serous retinal detachment and hypofluorescent choroidal dots may be observed. Usually 90% of these lesions resolve completely after 3 to 10 weeks and in some cases pigment epithelium changes develop.

Diagnosis
The diagnosis of Rickettioses is confirmed when positive serologic tests are found in patients with a compatible clinical presentation living or travelling in endemic areas. High antibody titer of a fourfold rise in convalescent serum may be used as diagnostic tests.

Treatment
Tetracyclines (25-50 mg/kg/day) chloramphenicol (50-75 mg/kg/day), doxycycline (200 mg/day) or ciprofloxacin (1.5 gr/day) are the most common antibiotics used for Rickettioses. The ocular involvement may also benefit from a topical corticosteroids and cycloplegic therapy, while retinal lesions will recover spontaneously or after antibiotic treatment. Systemic corticosteroid therapy is usually unnecessary.

Bartonellosis

Bartonella henselae, a gram negative aerobic bacillus, is the etiologic agent of cat-scratch disease, a worldwide infection of all ages and immunocompetent individuals. Humans are usually infected through a cat's scratch or bite, but also a bite by cat fleas may be the origin of infection. More common in children and young adults in warmer seasons, it usually presents with a wide range of systemic and ocular symptoms. Systemic signs and symptoms usually precede the ocular involvement and are constituted by the appearance, 3 to 10 days after inoculation of bartonella, of an erythematous papule on the skin on the site of inoculation. Seven to 14 days after exposure a follicular conjunctivitis may appear and, if the conjunctiva was the site of inoculation, even a granuloma may be found. Fourteen to 21 days after the inoculation regional lymphoadenopathy may occur which is usually associated with myalgias, fatigue and low-grade fever. The association of conjunctivits and regional lymphoadenopathy is well known as Parinaud's oculoglandular syndrome. The most frequent ocular manifestation is neuroretinits, usually unilateral and, if bilateral, quite asymmetric. It presents with optic disk edema, leakage from the retinal microvasculature and the formation of a macular star, because of the deposition of intraretinal lipids. In some cases optic disk edema may appear in combination with peripapillary serous retinal detachment. Rarely the posterior pole involvement may be characterized by the presence of a focal inflammatory mass and abnormal vascular network, either of the retina or of the optic disk, and this features is more characteristic of HIV seropositive patients. Cecocentral or paracentral scotoma or physiologic blind spot enlargement are the main alterations of the visual field, while fluorescein angiography usually presents a diffuse leakage from the optic nerve head along with the retinal vessels. Sometimes vascular occlusion with intraretinal haemorrhages and cotton-wool spots are present at the posterior pole. Anterior uveitis, intermediate uveitis, panuveits with retinal detachment and orbital abscess may also be observed in bartonellosis.

Diagnosis

Enzyme immunoassay and Western Blot, along with PCR arrays are usually used for diagnostic purpose, although past history of contact with cat should guide to the proper diagnosis.

Parinaud's syndrome is a clinical entity that may be due to numerous infection, including tularaemia, sporotrichosis, tuberculosis, syphilis, mononucleosis, coccidioidomycosis, while neuroretinitis with macular star may be observed in vascular disorders, toxoplasmosis, syphilis, tuberculosis, Lyme disease, viral infection.

Treatment

Bartonella henselae is sensitive to many antibiotics in vitro, but only aminoglycosides have bactericidal activity. Usually the therapy, if given, comprises a 10 to 14 days course of doxycicline, or ciprofloxacin, erythromycin, trimethoprim-sulfamethoxazole, rifampin and gentamicin

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Lymphoma and mascarade

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Classification of intraocular lymphoma

I. Metastatic disease from systemic lymphoma
   a. Hodgkin lymphoma [1]
   b. Mycosis fundoides [2]
   c. Burkitt lymphoma
   d. Multiple myeloma
   e. B-chronic lymphocytic leukemia [3]
   f. T- chronic lymphocytic leukemia

II. Metastatic disease from primary central nervous system lymphoma (PCNSL). Large diffuse B-cell lymphoma.

III. Primary intraocular lymphoma without evidence of other involvement.
   a. Large diffuse B-cell lymphoma
   b. T-cell lymphoma [4;5]
   c. T-cell rich B-cell lymphoma

Clinical diagnosis of primary intraocular lymphoma

I. Uveitis with unusual clinical features.
   a. Fails to respond to usual treatment for uveitis. [6;7]
   b. Presentation as a vitreitis only without retinal lesions can occur. [8]
   c. Homogeneity of the vitreous body without inflammatory stranding.
   d. Disproportionate lack of associated cystoid macular edema.
   e. Fluorescein angiography with granularity, blockage or leakage greater than predicted by clinical examination. [9;10]
   f. Mimickry of retinal vasculitis or necrotizing retinitis. [11;12]
   g. Multifocal, solid sub-RPE deposits [13;14]

II. Demographics
   a. Bilateral involvement is greater than 80%. [9;15]
   b. Average age 54 (range 36 – 90) in one series of 44 patients. [9]
   c. Appproximately 20% of PCNSL patients have intraocular involvement.

d. Approximately 80% of patients with PIOL will develop CNS lymphoma. Time from onset of ocular symptoms may influence time to CNS lesions.
   i. Average diagnosis one year after onset of ocular symptoms, 3 of 26 patients had CNS lymphoma. [16]
   ii. Average diagnosis 40 months after onset of symptoms, 29 of 44 patients had CNS lymphoma. [9]

Laboratory diagnosis of primary intraocular lymphoma

I. Acquisition of intraocular specimen.
   a. Needle aspiration. [17] Limited sample size, may disrupt cell structure less.
   b. Mechanized vitreous biopsy. Requires surgical procedure. Limited sample size. Less traumatic than needle aspiration.
   c. Pars plana vitrectomy. [18 19] Requires surgical procedure. Maximizes specimen size and permits multiple studies. [20] Attach syringe to short section of tubing to vitreous cutter.
      i. Small, undiluted specimen (0.5-1.0 ml) for cytology, PCR, culture.
      ii. Large, diluted specimen for flow cytometry, gene rearrangement.
   d. Chorioretinal biopsy of sub-RPE infiltrates. Chiba biopsy needle [21] or a long 27-gauge needle [22], clear silicone-tipped extrusion needle (preferred). [20] Diffuse retinal infiltrates can be cut from the retina with scissors and placed in formalin for histopathology.
   e. Attention to all aspects of specimen handling and processing is important. Transport in tissue culture medium may preserve viability. [23] HOPE medium can be used for long-distance transport. [24] Alternative: fixation 95% ethanol, filtration 5 micron filter for tissue block (not preferred). [25] Preparation of slides in lab by an automated cytocentrifuge [19] or by dropping onto coated slides. [26] Hematologic or Giemsa stains may be preferable to Papanicolau.

II. Analysis of biopsy specimen.
   a. Cytology. [7;17;18 27]
      i. Low frequency of diagnosis of lymphoma in diagnostic PPV series. [20;28] Second biopsies needed in some cases. [29 30] JHU: Confirmation of intraocular lymphoma in 42 (48.3%) of 87 eyes with a preoperative diagnosis of possible ocular lymphoma. [31] BPEI: 13 (46%) of 28 eyes.[20]

ii. Cytologic characteristics: irregular nuclear outline, multiple nucleoli, coarse chromatin. [32] Need for expert review. May contain abundant "reactive" lymphocytes masking malignant cells.

b. Immunohistochemistry and flow cytometry
   i. Slide-based method used concomitantly with cytology [25;32] to categorize cells by cell surface markers indicating lineage, function, and light-chain clonality. [19;23;26] May be less susceptible to false negative than cytology if cells degraded. [26] Visualization of color reaction when murine monoclonal antibody to surface marker is bound with equine biotylinated anti-murine immunoglobulin and exposed to avidin-biotin-peroxidase reaction.
   ii. FACS analysis: flow cytometry. [19;26;33] Also relies on antibody binding to cell surface markers. Automated. Permits more markers to be tested as 3 to 4 fluorescent antibodies with different colors can be used simultaneously.

c. Cytokines
   i. Ratio of IL-10 relative to IL-6 by ELISA testing. [34 35 36] IL-10 preferentially expressed by B-cell malignancies, IL-6 is produced by inflammatory B-cells. Utility is obviously limited to intraocular lymphoma with B-cell phenotypes.
   ii. Absolute value of IL-10 is affected by dilution of most vitreous diagnostic specimens. In undiluted vitreous, to measure the average IL-10 in 16 patients was 2352 pg/ml (range 70-5120). [9]

d. Molecular techniques
   i. PCR to amplify the complementary determining region (CDR3) of the immunoglobulin heavy chain (IgH). [37] Microdissection prior to PCR amplification increases the diagnostic yield. [38] Translocation between chromosomes 14 and 18 and gene rearrangement of the Bcl-2 protein also occurs. [37;39 40] Rearrangement of the T-cell receptor gamma gene applicable to intraocular T-cell lymphomas.[37] Gene rearrangement may be more sensitive that other techniques to diagnose PIOL. [41]

Treatment

I. Intraocular lymphoma associated with systemic lymphoma
   a. Treatment of primary malignancy.
   b. Usually combined with ocular irradiation, particularly if previously treated.

II. Intraocular lymphoma associated with primary central nervous system lymphoma
   a. Chemotherapy
      i. High-dose methotrexate > 1 g/m^2 up to 8 g/m^2 is the mainstay of therapy. [42]
      ii. MTX + a variety of other agents. Multiple regimens summarized in review article.[42]
   b. Irradiation of neuroaxis and eyes may be done. Often deferred until chemoresistance relapse occurs. Dementia can follow irradiation of the brain, particularly in elderly patients.
   c. Intra-arterial mannitol to open the blood-brain-barrier followed by intra-arterial chemotherapy may potentiate it.

III. Primary intraocular lymphoma.
   a. Treatment before CNS involvement diagnosed.
      i. Local. Usual treatment is irradiation. Average progression free survival in a multicenter European study was less in locally treated (5.5 m) than in systemically treated patients (12 m). [43]
      ii. Systemic. As for PCNSL. Often combined with irradiation.
   b. Treatment at time of CNS involvement. Calculated from time of onset of ocular symptoms, median survival was longer (60 m) in patients treated before CNS disease, than in patients only treated after CNS disease developed (35 m). [44] Some patients in this study received radiation therapy only.

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Intermediate / pars planitis

Pierre Labalette
France

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Birdshot retinochoroidpathy

Phuc LeHoang
France

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Ocular Sarcoidosis

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Sarcoidois is a multiorgan disease, characterized by its pathological hallmark, the non-caseating granuloma. The illness can be self limiting or chronic with episodic recurrences and remissions. The clinical course varies often significantly among individuals and ethnic groups which has helped fueling the hypothesis that sarcoidosis has more than one cause, each of which may promote a different pattern of illness.

Epidemiology
Sarcoidosis occurs world wide, with however a large diversity. The estimated prevalence ranges from 3 of 100,000 in Poland, to 64 per 100,000 in Sweden to 200 for Irish women living in London. The sarcoidosis related mortality has been estimated to be between 0.5% and 5% (Haimovici); approximately one fourth of those with chronic sarcoidosis die of respiratory failure.

Pathogenesis
The pathogenesis of sarcoidoisis remains an enigma. Two leading hypotheses have evolved regarding the etiology. One hypothesis is that sarcoidosis is most likely the result of exposure of a susceptible host to a potential etiologic agent. An alternative hypothesis cedes that sarcoidosis may be a clinical syndrome that includes a collection of different diseases, each with a different etiology.

Environmental factors: Reports of community outbreaks, a work related risk of sarcoidosis for health professionals strongly suggest that the disease is spread by person to person transmission or shared exposure to an environmental agent. Many microorganisms are known to induce a granulomatous inflammation and the fact that homogenates of human sarcoid tissue and cells (such as the Kveim-Siltzbach reagent) cause local and disseminated granulomas suggest that the cause of the disease might be infectious. None the less identification and final proof of an infectious agent are still lacking. Atypical myobacteria remain a prime suspect, however the results of varies studies have produced divergent results.
Genetic factors: The fact that sarcoidosis occurs more frequently in monozygotic that dizygotic twins suggests a genetic factor. In addition the presence of familial clusters of at least 19% in affected black families and 5% in white families support the hypothesis of a role of genetic factors. It appears as if a genetically predisposed host, exposed an environmental trigger may respond by an exuberant immune response

and the formation of granulomas. Thus the genetic factors might reside in the loci that influence the immune response, T-lymphocyte function or antigen presentation or recognition. Genes identified with an increased risk for the development of sarcoidosis are in class I HLA A1, and B8 in class II HLA-DR3.

The overall sequel in the pathogenesis suggested so far from both histologic as well inflammatory cells harvested by bronchoalveolar lavage is:
The first step is an alveolitis, where macrophages secrete proinflammatory cytokine like IL-1 and TNF in response to so far unknown environmental agent. In a genetically predisposed host that might lead to an exuberant accumulation of T-helper cells (CD4+), that by secreting IL-2 lead to further T-cell activation and an oligoclonal expansion. Chemotactic factors secreted by T-cells lead a local accumulation of macrophages, that might than aggregate and differentiate into epitheloid and multinucleated giant cells. Abundant T-cells and to lesser degree B-cells are interspersed among these inflammatory cells. In time a dense band of fibroblasts, mast cells, collagen fibers and proteoglycans start forming a rim around this ball-like cluster of cells. Fibrosis the ultimate outcome.

Clinical features
The clinical manifestation can show variable difference and may involve only one or multiple organ systems at a time.
The clinical course may be acute, sub-acute or chronic. A primary pulmonary involvement is seen in 15-40% of patients, with a large portion of these (12-35%) being asymptomatic at first. The majority (15-40%) of patients will however present with generalized complaints such as fatigue, anorexia, fever, and weight loss. In 20-50% with acute disease one might find the constellation of erythema nodosum, bilaterale hilar lymphadenopathy and polyathralgien known as Loefgren's syndrome. Heerfordt-Waldenstrom syndrome the other sign of an acute disease is characterized by the presence fever, parotid enlargement and uveitis. The acute symptoms may in some instances resolve after some time with often minimal damage or become chronic.
Approximately 40-75% of patients however show an insidious onset of the disease.
Overall clinical symptoms may include (Sarcoidosis Dahl AA et al. http://www.emedicine.com/oph/topic451.htm)
Pulmonary involvement may cause: dyspnea, retrosternal chest pain, and cough.
Extrapulmonary involvement: includes lymphadenopathy, skin lesions, and upper respiratory, marrow and splenic, hepatic, renal, neurologic, musculoskeletal, cardiac, and endocrine manifestations.
Neurologic sarcoidosis: General symptoms include headache, dizziness, facial weakness, hemiparesis, paresthesias, gait disturbances, impaired memory, decreased hearing, seizures, and rarely psychiatric symptoms.

Neuro-ophthalmologic involvement: Symptoms include diplopia from cranial nerve palsies and decreased vision with or without scotoma from optic nerve infiltration or edema. Visual symptoms from glaucomatous optic nerve damage may be superimposed.
Ocular sarcoidosis: Symptoms from uveitis include pain, hyperemia, photophobia, blurred vision, floaters, redness, and scotomata. Dry eye symptoms such as ocular discomfort, burning itching are frequently seen in case of periocular lesions or involvement of the lacrimal gland. Orbital involvement may cause proptosis and diplopia.

Non-Ocular disease.
Thorax: A respiratory track involvement is seen in most patients at some stage of the disease. An interstitial lung disorder involving the alveoli as well as the bronchioles is the most common feature, leading to restricted lung volumes. Granulomatous involvement is also frequently seen. Approximately half of patients show granulomas in endobronchial biopsies. The progressive fibrotic destruction of the parenchyma leading to respiratory failure is the leading cause of mortality from sarcoidosis. The staging of the disease is based on radiologic involvement if the parenchymal and lymphatic involvement.

Lymphatic system
Intrathoracic and peripheral lymphnode involvement is seen in 75-90% of patients. Involved lymphnodes are usually nontender, and may in some instances become disfiguring. Gallium scanning allows detection of lymphnode involvement. The biopsy of involved lymph nodes usually show granulomata.

Skin
Cutaneous involvement in sarcoidosis can vary from raised, tender, livid nodules of erythema nodosum, to cutaneous granulomata that may be maculopapular, raised and vesicular eruptions to scars. Some kind of a skin involvement is seen in up to 25% of patients. Lupus pernio, indurated purple lesions, represent a classic granulomatous manifestation which may be seen on the cheeks, noose, lips and ears.

Nervous system
Involvement of the nervous system is seen in approximately 5% of patients. Virtually every part of the nervous system might be affected. Seizures, neuropsychiatric and personal disturbances may be present in neurosarcoidosis. Also aseptic meningitis, masquerading a meningioma or monoclonal infiltrate can be part of a neurosarcoidosis. The most commonly affected nerve is the facial nerve, however the optic nerve, third and fourth or sixth cranial nerves may also be seen.

Liver
Liver involvement is frequent (40-70%), but rarely clinically significant. However as seen in one of our patients, biopsies of the liver showing granulomatous infiltrates might in some instances be only way to finally confirm the diagnosis of sarcoidosis.

Ocular involvement
The number reported on the presence of an ocular disease in sarcoidosis vary quite significantly and range from 25- approximately 50%. (Nussenblatt) The ocular disease is usually bilateral, however it might also be unilateral or be highly asymmetric. Since the easiest accessible part of the eye, for a biopsy special attention should be paid to a possible involvement of the conjunctiva or the lacrimal gland. Both of which are involved in 7-25%.(Nussenblatt)

Conjunctiva
Conjunctival granulomas can often be hard to distinguish from follicules or papillae and are in most instances asymptomatic. Cicatrizing conjunctivitis and symblepharon formation are very rare. Keratoconjunctivitis sicca usually results from lacrimal gland involvement.

Uvea
The most common form of sarcoidosis in the eye is the **anterior uveitis**. It occurs in almost 75% of patients with an ocular involvement. Fifty three to sixty % will develop a chronic granulomatous uveitis. (Nussenblatt) Most of these will show "mutton fat", granulomatous partially pigmented keratic precipitates. Chronic anterior uveitis with an insidious onset, frequently leads to band keratopathy, cataract and secondary glaucoma, if not adequately treated. However also fine non- granulomatous endothelial deposits can be seen, especially in cases of an acute anterior uveitis, which occurs in 15-45% of an ocular involvement. Chronic forms generally occurs in patients with sarcoidosis in the fourth through sixth decade, but may also be seen in much younger patients.

Iris nodules, reported to be present in up to 12.5%, may be seen either at the pupillary margins (Koeppe nodules), which are non-pathognomonic or the iris surface (Busacca nodules). These areas are predisposed areas for the development of posterior synechiae and sector cataract.
If the anterior uveitis is associated with erythema nodosum, bilateral hilar adenopathy it often tends to self-limiting.
Posterior uveitis often shows an insidious onset. It is less common then anterior uveitis, 6-33%, but far more disabling. In most instances, to variable degree, also an anterior involvement is seen. Cellular infiltrates, may be evenly dispersed or may be aggregated into clumps (snowballs) and located in the inferior vitreous. These cells usually consist of T-lymphoctyes. In instances where these vitreous infiltrates primarily affect the lower part of the vitreous and pars plana, it might be indistinguishable from

idiopathic intermediate uveitis. In cases of a posterior uveitis **periphlebitis** to some degree is usually seen. Occasionally the perivenous exsudates may that intense, that they compare to "candle wax drippings" ("taches de bougie"). Periarteritis is rare.
Deep yellow infiltrates, resembling Dalen-Fuchs nodules and retinal pigment epithelial alterations are present in 36% of patients with posterior inflammation. The total extent of **subretinal or choriodal involvement** may in be evanescent, especially in early stages, and seen only in fluorescein or ICG angiogram. These yellowish nodules most commonly are flat and dispersed in the mid periphery. They may resemble lesions seen in birdshot retinochoroidopathy, or be punched out like in multifocal choroiditis. Large solitary granulomas are infrequent and have to be distinguished from choroidal metastases. If they are present centrally large subretinal neovascularisations may follow. **Optic nerve** involvement is mostly seen as a mild papillary edema. However sarcoid granulomas affecting the optic disk as well as retrobulbar neuritis have been described.

Prognosis

The prognosis of the patient is based on the initial clinical presentation. Stage I disease, defined by the presence of hilar adenopathy without parenchymal infiltrates, remits in 60-80%, stage II, hilar adenopathy with parenchymal infiltrates, remits in 50-60% and stage III, parenchymal infiltrates without hilar adenopathy, remits in 50%. Patients with Löfgren's syndrom have the best prognosis. An average of 50% will develop at least a mild degree of permanent organ dysfunction and even in patients that primarily respond to corticosteroids, approximately 25% will relapse, once the therapy is discontinued. Poor prognosis is seen especially if the onset of the disease is after the age of 40, symptoms that last more than 6 months and involvement of more than three organ systems. For the ocular disease, patients with a chronic disease that are not adequately treated are at a high risk to develop posterior synechiae, cataract, secondary glaucoma ultimately leading to a phthisis bulbi; and optic disk or chronic macular edema.

Treatment

Due to the heterogeneity of the disease, treating patients with sarcoidosis is a challenge. As a general rule treatment should be initiated as first line treatment in ocular, neurologic or cardiac sarcoidosis. Malignant hypercalcemia, progressive stage II disease, should also be treated. **Corticosteroids** remain to be the mainstay therapy. Current protocols suggest the use of 30-40mg of prednisone daily over a period of 8-12 weeks, with gradual tapering of the dose to 10-20mg every other day over a period of 6-12 months to establish the minimal effective dose. However a recent study has shown that in chronic forms corticosteroids have short-term benefit, thus a variety of other pharmacologic approaches have been tested. Among these especially **methotrexate** has shown to be effective, in both reducing the dose of corticosteroids necessary as well in patients with refractory or unable to bear the

suggested corticosteroid therapy. Despite the ability of **cyclosporine** to suppress T-cell activity, studies on its efficacy in sarcoidosis have proved contradictory and in some studies disappointing. However low-dose Cyclosporine therapy has also been used successfully in patients with refractory ocular sarcoidosis. **Chlorambucil** and **Azathiosprine** treatment has also been applied successfully for corticosteroid resistant neurosarcoidosis patients.

For the **ocular disease**, in cases of mild **acute anterior** uveitis local corticosteroids in addition to cycloplegics might be used. However if no adequate response is seen, in cases of bilateral involvement or in the intermediate uveitis or retinal disease periocular or systemic corticosteroid therapy might be necessary. Treatment of **chronic disease** can be quite challenging. Initial high dose corticosteroid (1mg/kg/d) is initiated, followed by slow tapering of the dose (as mentioned above). However in cases of prolonged disease or intolerance to the systemic corticosteroid therapy the use of steroid sparing agents like methotrexate or cyclosporine might be necessary. Even radiotherapy has already been applied for sarcoidosis of the anterior visual pathway. Patients with ocular sarcoidosis frequently suffer from recurrent episodes of their disease also special care has to be taken in the case of surgery, where acute exacerbations of the inflammation can be seen in the ultimate perioperative period. Thus a high perioperative corticosteroidtherapy should be considered in patients in need for lensectomy or pars plana vitrectomy. (Nussenblatt).

Diagnosis

Laboratory investigations.

Radiology: Abnormal radiologic findings of the **chest x-ray** are found in a large portion of sarcoid patients. Changes are usually bilateral and staging of sarcoidosis follows the radiologic findings.

However especially in instances of only mild involvement of the lungs **high-resolution computed tomography scanning (hr-CT)** proves to be superior to conservative chest x-rays. In a recent report Kosmorsky et al. described three patients with negative chest x-ray, where using hr-CT the presence of paratracheal and para-aortic lymphadenopathy consistent with sarcoidosis was revealed. **Gallium Scan**, even though highly sensitive, is not specific for sarcoidosis. Its diagnostic sensitivity is increased from 38-83% to over 90% if combined with an elevated serum ACE level. After injection of gallium-67 citrate it localizes to areas of inflammatory activity. Positive results may be obtained in lymphoma, tuberculosis, carcinoma or silicosis. Lacrimal and/or parotid gland uptake is very common and may be seen in 60-87% of patients. Increased of gallium-67 in the lacrimal, parotid and submandibular gland is known as Panda sign. It may be used to evaluate patients with a normal chest X-ray and clinical manifestations suggesting sarcoidosis. It may also help in finding a biopsy site and to some degree to evaluate therapeutic effect of treatment. The uptake of gallium decreased after corticosteroid therapy.

Mediastinoscopy in addition to **Transbronchial Biopsy** are ways to finally confirm the diagnosis of sarcoidosis by obtaining tissue samples, where the presence of non-caseating granulomas can be demonstrated**. Bronchoalveolar lavage** (BAL)may also be used to harvest inflammatory cells. The ratio between CD4/CD8 cells might be indicative of the presence of a sarcoidosis. A ratio of 3.5 has a sensitivity of 52% and a specificity of 94%.(Costabel et al.). Thus a positive BAL might obviate the need for transbronchial biopsy in 40-60% of cases. (Constabel et al.)

Serologic test

Angiotensin converting enzyme (ACE)

ACE is hydrolase that cleaves angiotensin I, converting it angiotensin II. ACE is expressed on the luminal surface of pulmonary vascular endothelial cells and from cells of the alveolar macrophages. The major source of ACE in sarcoidosis are the epitheloid cells in sarcoid lymph nodes. Thus it appears as if the level of serum ACE reflects the total body mass of ACE producing granulomas. In a series on 221 uveitis patients Baarsma et al found that the sensitivity of the test was 84%, the specificity was 95% and its predictive value was 47% in the presence of an elevated serum level of above 50 U/l. Measuring local ACE levels in the aqueous humor of uveitis patients has also revealed to be diagnostic in sarcoid patients. Special care has to be taken when ACE levels are evaluated in children. In these patients higher ACE levels than those found in adults are physiological.

Lysozyme (LZM)

Lysozyme is low molecular weight molecule secreted from monocytes and polymorph nuclear cells. Elevated lysozyme levels are however far less specific for sarcoidosis, than ACE levels. In the study by Baarsma et al. a specificity of 76% for LZM above 8mg/L is described.

Hypercalcemia and Hypercalciuria

Due increases in the amount of 1,25 di-hydroxyvitamin D produced by alveolar macrophages and granulomatous tissue. This overproduction of 1.25 di-hydroxyvitamin D leads to an increased absorption of calcium, enhanced bone resorption , and resultant hypercalciuria with or without hypercalcemia.

Skin tests

Cutaneous anergy due to an impaired cutaneous delayed type of hypersensibilty to such antigens as Candida sp., mumps and Trichophyton which is present in approximately 50% of patients. A previous positive Tuberculin test may thus become negative in the course of the disease.

Kveim Siltzbach Reaction: In the Kveim Siltzbach reaction an intradermal injection

of heat-steralized human suspension of sarcoid tissue from lymph nodes or spleen is given. A reaction is considered positive, if after 4-6 weeks a non-caseating granuloma is present at the site of the injection.

BEHÇET'S DISEASE

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History, Epidemiology, and Diagnosis

Behçet's disease (BD) is a chronic relapsing inflammatory disease with multisystemic manifestations. Although Hippocrates was probably the first to recognize the characteristic symptoms, the disease is named after Professor Hulusi Behçet, a Turkish dermatologist, who described the symptom complex of recurrent aphthous oral ulcer, genital ulcer, and uveitis as a distinct entity in 1937.

Although BD is a universal disorder, it is much more prevalent in the Mediterranean area, the Middle East and the Far East. In Turkey, the prevalence rate has been found to be 80-420 patients per 100,000 inhabitants. The prevalence rate of the disease is 2-30/100,000 in the Asian continent and 0.1-7.5/100,000 in Europe and the USA.

Behçet's disease has a wide spectrum of clinical manifestations and there is no pathognomonic diagnostic test. Therefore, the diagnosis is based on identification of its typical clinical features. At least 5 sets of diagnostic criteria had been in use until the International Study Group (ISG) for BD Criteria were proposed in 1990. According to this set of criteria, the diagnosis of BD is based on observation of oral ulcerations recurring at least three times a year plus two of the following four lesions: recurrent aphthous genital ulcerations; eye inflammations including anterior or posterior uveitis or retinal vasculitis; skin lesions including erythema nodosum, papulopustular lesions, pseudofolliculitis or acneiform nodules, and a positive pathergy test defined as $\geq$ 2 mm erythema occurring 48 hours after a skin prick by a sterile 20-22G needle. The ISG for BD has later recommended that the ISG scheme be known as "classification" criteria since it ensures uniformity of the patient groups in studies of the disease rather than the diagnosis of individual patients. Oral ulcers represent the initial symptom in the majority of patients and fulfillment of the ISG criteria may be delayed.

Ophthalmic Features

The reported frequency of ocular involvement varies greatly depending on the patient population studied. In the most recent field survey conducted in Istanbul, the rate of ocular involvement was found to be 25%. Higher figures of up to 98% have been reported in hospital-based populations.

The onset of ocular disease is in the third and fourth decades of life. There is a male predominance with a male-to-female ratio of 2:1 to 5.2:1 in series reported from Turkey and the Middle East. The majority of patients have bilateral involvement although the disease may not run a similar course in both eyes.

Since Behçet uveitis typically starts with an explosive attack, most patients are symptomatic from the beginning. Depending on the type and severity of uveitis, patients may complain of redness, pain, photophobia, blurred vision or significant visual loss. There are also patients who are asymptomatic despite detection of ocular findings on routine control examinations or even only by fluorescein angiography.

The natural course of the disease is characterized by spontaneous remissions and relapses. The frequency and timing of exacerbations are unpredictable although some patients seem to have more frequent attacks in the spring. Our clinical observations suggest that emotional stress of any type may trigger exacerbations. Dental procedures, bacterial or viral infections also seem to be associated with exacerbations of uveitis. Our patients do not report any association with any type of food intake.

Anterior or posterior segment of the eye, or more commonly both may be inflamed unilaterally or bilaterally at a given episode of activation. A nongranulomatous panuveitis with retinal vasculitis is the most common form of ocular involvement. Fine KPs and freely moving fine aqueous cells are seen with or without perilimbal injection. Increased flare and significant amounts of fibrin in the aqueous humor are sometimes seen during severe attacks. The recurrent sterile hypopyon described originally by Behçet has been reported in 10-30% of the patients. The presence of a hypopyon denotes a severe attack usually involving the posterior segment as well. Because of the transient nature of the hypopyon the actual frequency of its occurence is probably higher than is noted in the medical records. The “cold” hypopyon, i.e., absence of conjunctival hyperemia, is a characteristic feature of BD. Another characteristic feature is that the Behçet hypopyon is not sticky. It shifts freely with head positioning and dissolves when the patient lies in a supine position.

Fundus changes associated with Behçet uveitis are protean. During a severe attack significant vitreous haze may obscure the details of the fundus for several days. Retinal

infiltrates of various sizes and locations are seen with or without accompanying hemorrhages. These lesions appear suddenly and may resolve spontaneously without leaving scars. When extensive, retinitis may have the appearance of a virally induced lesion. However, in contrast to ARN, Behçet retinitis does not have a predilection for peripheral fundus and has a multifocal pattern that does not progress with or without treatment. Sometimes an exudative retinal detachment is seen, confined to the macula or extending to the periphery. Arteriolar attenuation, venous engorgement and tortuosity may be the only vascular signs of a mild attack. The more typical hemorrhagic vasculitis of BD may resemble the fulminant form of CMV retinitis, especially when vitritis is minimal. However, more commonly, there is significant vitreous haze in BD. Even though retinal vasculitis of BD involves both arteries and veins, periphlebitis is more common and appears in a diffuse rather than a segmental pattern. Sheathing and occlusion of peripheral retinal veins and arterioles are the typical features of Behçet fundus. Involvement of the capillary bed may be evident by superficial lesions that resemble soft exudates, diffuse retinal edema, and by isolated dot and blot hemorrhages that do not follow a BRVO pattern.

The optic disc is invarably involved in BD. Hyperemia of the disc with blurred margins is a typical finding during inflammatory episodes. It is important to differentiate papilledema due to increased intracranial pressure in Neuro-Behçet from inflammatory edema associated with ocular Behçet. Isolated papillitis may also occur in BD. Hemorrhagic papillitis is the most severe form. The disc becomes pale in the late stages of the disease.

Branch retinal vein occlusion without any sign of uveitis is another form of ocular involvement in BD. Central retinal vein occlusion is less common.

Neovascularization is a significant complication of BD occurring in around 5% of the eyes. Disc neovascularization is more commonly induced by severe and persistent intraocular inflammation. The characteristic finding on fluorescein angiography is diffuse microvascular leakage in these eyes, whereas NVE is almost always associated with significant capillary nonperfusion.

Macular involvement is a significant cause of visual impairment in BD. Retinitis and/or hemorrhage involving the macula, diffuse or cystoid macular edema, degenerative changes, epiretinal membrane formation and macular hole may all be seen in BD. Although we have seen development of a macular hole after a single attack of uveitis, repeated attacks increase the risk of significant maculopathy.

Depending on the severity and the number of uveitis attacks, permanent damage to the intraocular structures ensues. Cataract and posterior synechiae are the most

common complications in the anterior segment. Other less common complications include glaucoma, intravitreal hemorrhage, retinal tear, retinal detachment, and phthisis bulbi. The end-stage fundus picture is characterized by optic atrophy, gliotic sheathing of retinal vessels, occluded vessels that look like white cords, diffuse atrophy and gliosis of the retina with variable scarring and pigmentation resembling retinitis pigmentosa. The vitreous is remarkably clear at this stage

External eye findings: Conjunctivitis, conjunctival ulcers, episcleritis, and keratitis are the rare ocular manifestations of the disease.

Pathogenesis

The etiopathogenessis of BD remains unclear. An up-regulated inflammatory response is an important feature of BD and many of its characteristic recurrent manifestations overlap with those of autoinflammatory diseases. The increased responsiveness to minor injury as seen in the classical skin pathergy reaction, has been observed at other body sites as well as at the cellular level. The enhanced inflammatory response and over-expression of proinflammatory cytokines observed in BD are compatible with the findings in other autoinflammatory disorders. Several immunological alterations have been found in BD, including a higher percentage of γδ T cells, oligoclonal T cell expansions, spontaneous or induced hypersecretion of Th1 type proinflammatory cytokines, *in vivo* priming of neutrophils, increased neutrophil chemotaxis, and increased numbers of activated and memory B cells as well as NK cells.. Behçet's disease is closely associated with HLA-B51 in endemic areas. The contribution of the HLA-B locus to the overall genetic susceptibility to BD has been estimated to be less than 20% and other susceptibility loci need to be identified. It has been postulated that environmental factors cause an antigen-driven specific inflammatory response superimposed on enhanced innate immune reactivity. The resultant vascular endothelial cell activation and injury may contribute to the occlusive vasculopathy that is associated with various manifestations of the disease.

Prognosis and Treatment

The frequency and severity of uveitis attacks vary from patient to patient. Furthermore, the unpredictability of the disease course in a given patient, makes evaluation of various treatment modalities difficult. Several risk factors have been postulated as indicators of poor visual prognosis, including male sex, young age at onset, skin lesions, arthritis, neurologic involvement, vascular thrombosis, and posterior uveitis attacks. In a retrospective analysis of 880 patients with Behçet uveitis we have found that male patients had a younger age at onset, had more severe disease, a worse

potential visual acuity at presentation and also a higher risk of loosing vision over time. Kaplan-Meier survival analysis showed that the risks of loosing vision at 5 and 10 years for males and females were 21% vs. 10% and 30% vs. 17%, respectively (log-rank=16.75, p=0.0001). In both sexes the survival rate remained constant after around 10 years. However, visual prognosis improved in the 1990s compared to the 1980s due to an earlier and more aggressive use of immunosuppressive therapy.

There is no single therapeutic regimen uniformly effective in all patients with BD. The choice among various regimens should be made on an individual basis. Laterality of the involvement, disease stage and magnitude of permanent damage at presentation, potential side effects of therapeutic agents, compliance of the patient are some of the several parameters that are taken into account in making this decision.

In the conventional therapeutic approach, corticosteroids are used for the treatment of acute intraocular inflammation. However, corticosteroid monotherapy often fails to prevent recurrences and is associated with a high rate of side effects if used as a maintenance therapy at high doses. Immunosuppressive drugs are indicated for long-term management.

Azathioprine at a dose of 2.5mg/kg/day has been shown to be superior to placebo in controlling progression of eye disease and to be associated with a better long-term prognosis especially if administered within 2 years of the disease onset. Mycophenolate may be an option in case of azathioprine intolerance.

Cyclosporine A at an initial dose of 5mg/kg/day may be used for the treatment of acute uveitis due to its rapid action. Several trials have shown its superiority to the conventional immunosuppressive agents, including colchicine, cyclophosphamide, and chlorambucil. The combination of cyclosporine A and azathioprine is more effective in controlling ocular disease than monotherapy with either drug. An abrupt cessation or even rapid tapering of cyclosporine A may cause a rebound attack. Therefore, it must be used with caution in noncompliant patients. Likewise, cyclosporine A is best avoided in patients with neuroBehçet due to its potential neurotoxicity.

Cyclophosphamide is used for the treatment of vascular involvement of BD and for central nervous system vasculitis. Its long-term use is limited in male patients with uveitis because of the risk of irreversible infertility.

Although chlorambucil has been abandoned by many authors due to its bone marrow toxicity, a study from Turkey reported that short-term therapy was effective in controlling the disease in two-thirds of the patients with refractory uveitis.

In recent years, biologic agents have been used for the treatment of Behçet uveitis. In an uncontrolled prospective study, Kötter et al reported a response rate of 92% in patients treated with interferon alfa-2a for sight threatening posterior uveitis or retinal vasculitis. Furthermore, 40% of their patients remained disease free after discontinuation of treatment. We have employed interferon alfa-2a treatment in patients unresponsive to conventional immunosuppressive therapy and obtained a partial or complete response in 91% of our patients.

Anti-TNF agents, infliximab and etanercept have also been used in uncontrolled clinical trials. Infliximab has been shown to have a rapid antiinflammatory effect and reduce the frequency of uveitis attacks. In an open trial, we administered 4 infusions of infliximab (5mg/kg) to 13 patients with Behçet uveitis refractory to the combined regimen of azathioprine, cyclosporin, and corticosteroid. Only 4 patients remained attack-free during the infusion period and all but one patient continued to have uveitis attacks during the observation period, i.e., after the discontinuation of infliximab. Treatment needs to be continued with infusions at 6-8 week intervals to prevent relapses.

Both interferon alfa and infliximab have potent and rapid anti-inflammatory effects. We do not use systemic corticosteroids when we administer these agents for the treatment of acute exacerbations.

In conclusion, the ideal therapy of Behçet uveitis has not yet been found and despite new alternatives, conventional immunosuppressives are still widely used. Comparative trials are needed to determine the optimal long-term therapeutic regimen in BD.

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Use of corticosteroids in uveitis

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1. Introduction

The Systematic Uveitis Nomenclature (SUN) Working Group classifies uveitis into four categories: anterior, intermediate, posterior, and panuveitis. Community-based ophthalmologists, in contrast to those at academic centers, see a higher proportion of anterior uveitis and lower proportions of the other three types. All ophthalmologists should understand the different categories of corticosteroids (topical, periocular, intravitreal, oral, and intravenous), the role for each in the treatment of different types of uveitis, the different formulations and potencies of corticosteroids within a given category, and the potential side effects of these drugs.

Principles of corticosteroid therapy in patients with uveitis are based on the goals of therapy, an understanding of ocular pharmacology, dosing regimens, and the minimization of side effects. Typically, corticosteroids are initiated at a high or frequent dose to suppress inflammation rapidly and then gradually tapered. The ophthalmologist must decide if maintenance (suppressive) therapy is warranted, or if the treatment can be discontinued altogether.

2. Local Therapy

Local therapy includes topical, periocular, and intravitreal corticosteroids. Such therapy has the advantage of minimizing (but not necessarily eliminating) systemic side effects and is often therefore most effective in the treatment of isolated ocular inflammation. Disadvantages of local therapy includes fluctuating drug levels, infection, hemorrhage, pain, inconvenience of repeated injections (if short-acting), local toxicity (sterile endophthalmitis, retinal toxicity), the need for a second procedure for bilateral disease, and a lack of demonstrated efficacy in controlled clinical trials for many conditions. Ptosis and corneal melting can occur during topical therapy. Rarely, the use of frequent topical corticosteroids can induce adrenal suppression, especially in children.

The potency of topical corticosteroids is affected by drug concentration, the chemical formulation of corticosteroid, and the composition of the vehicle; small modifications in preparations can produce a more than 20-fold difference in intraocular drug concentration. Prednisolone acetate 1% remains most potent formulation. However, despite efforts to separate the anti-inflammatory effects from the tendency to increase intraocular pressure, the the risk corticosteroid-induced glaucoma is also greatest with prednisolone acetate. Patients with more mild anterior

uveitis may respond adequately to less potent preparations, such as rimexolone 1%, loteprednol 0.5%, or fluorometholone 0.1%.

Periocular corticosteroid injections are usually given as triamcinolone acetonide 20-40 mg. The injections may be given either anteriorly (subconjunctival) or posteriorly (posterior sub-tenon's or retrobulbar), but the latter are more useful for the treatment of intermediate uveitis or cystoid macular edema (CME). Complications include glaucoma (in as little as 7-10 days), cataract (in as little as 4 months), orbital fat atrophy, ptosis, restriction of eye movement, globe perforation, scleral melting, adrenal suppression, and hyperglycemia. The role of periocular corticosteroids in the treatment of scleritis is controversial because of the risk of scleral melting, and most experts would limit their role to cases of diffuse anterior scleritis unresponsive to other therapies.

Intravitreous corticosteroid injections may induce glaucoma (acute or chronic), cataract, and endophthalmitis. Sterile endopthalmitis has been reported to occur at a rate 0.2-6.9% per injection and may present with pseudohypopyon. The use of preservative-free triamcinolone acetonide may reduce this risk. Infectious endophthalmitis has been reported to occur at a rate of 0.5-0.9% per injection and can be associated with vitreous wick syndrome. Only single-use vials should be used, and placement of a lid speculum and appropriate use of antibiotic drops (including povidone-iodine 5%) will reduce the risk of intraocular contamination with ocular surface or lid flora.

The intraocular corticosteroid implant (Retisert™, fluocinolone 0.59 mg) is a sustained-release delivery system designed to deliver drug at a relatively constant rate over 2.5 years, providing a significant advantage over other intraocular corticosteroids. Complications of the surgery include infection, retinal detachment, vitreous hemorrhage, and exposure of the strut. Nearly all patients develop a visually significant cataract in the implanted eye. Roughly half of all implanted eyes develop glaucoma, and two-thirds require glaucoma surgery.

3. Systemic therapy

Systemic therapy include oral and intravenous corticosteroids. Pulsed intravenous corticosteroids (methylprednisolone sodium succinate 1 gram/day for three consecutive days) are often useful in treating severe posterior and panuveitis, but because the duration of effect is limited, must be followed by treatment with high-dose oral corticosteroids.

Oral corticosteroids should be initiated at high initial doses until the uveitis is suppressed, then gradually tapered. The dose should generally not exceed 1 mg/dg/day for prednisone (methylprednisolone is also used; the conversion factor is 5 mg/prednisone= 4 mg methylprednisolone).. For chronic disease requiring suppressive therapy, the target dose is $\leq$ 10 mg prednisone/day; higher maintenance doses are associated with intolerable long-term side effects.

Side effects of oral corticosteroids can be categorized as mild, moderate (requiring dose adjustment or other intervention), and severe (requiring discontinuation or marked dose reduction). Mild side effects include cushingoid habitus, mood alteration and sleeplessness, capillary fragility, impaired wound healing, cataracts, and elevated IOP. Moderate side effects include weight gain and obesity, hypertension, hyperglycemia, hyperlipidema, and osteoporosis. Severe side effects include growth suppression in children, psychosis, diabetes, myopathy, and ischemic necrosis of bone.

All patients treated with oral corticosteroids should also receive calcium with vitamin-D to reduce the risk of osteoporosis. Systemic monitoring should include periodic weight, blood pressure, and blood glucose measurements, and patients on chronic therapy should undergo a yearly bone densitometry and lipid profile.

4. Treatment of specific diseases

4.1 Anterior uveitis

Acute & chronic anterior uveitis should be treated with intensive topical corticosteroids, typically at least every two hours initially. The addition of a "loading dose" at bedtime and on awakening can he helpful. Recalcitrant disease may respond to a short course of oral corticosteroids and/or a periocular corticosteroid injection. Cycloplegic drops are often necessary to reduce ciliary spasm and the risk of posterior synechiae formation

4.2 Intermediate uveitis

Intermediate uveitis such as pars planitis syndrome often does not require treatment if not macular edema or visually significant floaters are present; "snowballs" or peripheral retinal vasculitis alone are not necessarily indications for treatment. Topical corticosteroids do not penetrate well to the vitreous cavity and are generally not effective. Either regional corticosteroid injections or oral corticosteroids can be used to treat macular edema. Chronic intermediate uveitis may respond well to the intraocular fluocinolone implant.

4.3 Posterior and panuveitis

Posterior uveitis must be treated according to the specific disease. For example, serpiginous choroidopathy, multifocal choroiditis with panuveitis, and birdshot chorioretinopathy may respond initially to oral or periocular corticosteroids, but systemic immunosuppressive therapy, especially with alkylating agents, offers the best hope for long-term, drug-free remission. Bechet's disease has a poor long-term outcome when treated with oral corticosteroids alone, and early use of immunosuppressive therapy is indicated. In contrast, some types of posterior uveitis, such as multiple evanescent white dot syndrome or acute posterior multifocal placoid

pigment epitheliopathy, have a favorable long-term course and corticosteroid therapy has not been proven beneficial.

5. Clinical trials

The Multicenter Uveitis Steroid Trial (MUST) is a National Eye Institute-sponsored study that compares the intraocular fluocinolone implant to systemic therapy (low-dose oral corticosteroids and/or immunosuppressive therapy) for the treatment of severe non-infectious intermediate, posterior, or panuveitis.

Other clinical trials currently in progress include a sustained-release form of dexamethasone, designed to last for approximately six months; the drug is injected through a special delivery system as an in-office procedure.

Management strategies for chronic uveitis

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General considerations

Chronic uveitis is a potentially blinding condition, especially in young patients (10% of all cases of blindness). The rate of complications remains particularly high. Therefore, it is now accepted that even low-grade inflammation may result in permanent visual loss after a few months or a few years, depending on the etiology of uveitis. This high ocular morbidity is mainly associated with uncontrolled glaucoma, severe hypotony and / or different macular disorders.

Exclude an infectious condition

The use of specific strategies, when required, or immunosuppressive regimens, when an infectious condition has been excluded, is the only way to avoid a poor visual outcome.

Etiologic orientation, based on molecular techniques and specialized investigations is the most challenging issue and a major preliminary step before any further therapeutic consideration. CMV-associated anterior uveitis is an interesting example. Visual loss due to recurrent attacks and permanent glaucoma occurs in the absence of specific antiviral therapy. All immunomodulatory approaches and surgical strategies will be inefficient if viral infection is not significantly controlled. Whipple's disease, tuberculosis and different types of nonnecrotizing herpetic retinopathies are other masquerading conditions.

Evaluate the severity of disease

Different molecules are now available but their choice should be based on a number of considerations. All demographic and clinical characteristics must be considered.

These include the level and location of uveitis, clinical symptoms and complaints, BCVA, potential improvement, general health and compliance. Force of therapeutic options should be discussed in the front of potential risk factors in children or the elderly.

Therefore, juvenile idiopathic arthritis-associated uveitis is the best example of a chronic blinding condition in children, whereas birdshot retinochoroidopathy or serpiginous choroiditis are good examples in adults.

A global therapeutic strategy

Medical management

- Topical medications
- Periocular or intravitreal injections of corticosteroids
- Fluocinolone acetonide implant and other IVT devices
- Systemic corticosteroids
- Systemic immunosuppressors and immunomodulators
- Laser photocoagulation of ischemic retina
- Anti-VEGF for neovascular choroiditis

Surgical management

- Cataract
- Glaucoma
- ERM
- Retinal detachment

Immunosuppressive or immunomodulatory drugs

- Antimetabolites
  - Azathioprine
  - Methotrexate
  - Mycophenolate mofetil
  - Leflunomide

- T-cell inhibitors
  - Cyclosporine A
  - Tacrolimus
  - Sirolimus

- Alkylating agents
  - Cyclophosphamide
  - Chlorambucil (high toxicity+++)

- Biological agents
  - Interferon alpha
  - Anti-TNFα
  - Daclizumab
  - IvIg
  - Anakinra

Goals and indications of immunosuppressive strategies
Achieve, as soon as possible, the best control of intraocular inflammation by using a gradual algorithm.

International Uveitis Study Group guidelines :

- Absolute indications : Sympathetic ophthalmia, Vogt-Koyanagi-Harada disease, Rheumatoid sclerouveitis and Behçet's disease
- Relative indications : intermediate uveitis, retinal vasculitis, JIA-associated uveitis and idiopathic chronic uveitis

American Uveitis Society consensus :

- Ocular cicatricial pemphigoid, Necrotizing scleritis
- SO
- Serpiginous
- Behçet's disease
- Birdshot retinochoroidopathy
- JIA

Monitoring
Monitor anterior segment inflammation (Laser flare meter) and posterior segment inflammation (OCT / fluorescein and ICG angiography / Visual field)
Follow laboratory results
Communicate with the primary care physician

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New therapeutic modalities and monoclonals

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Core Messages

- Uveitis patients with severe sight threatening disease are conventionally treated with antiinflammatory and immunosuppressive therapy
- Immunosuppressive therapies include antimetabolites, antibiotics and calcineurin inhibitors; they all have generalized effects on the organism and are burdened with various side effects
- "Biologicals" target the autoaggressive immune response more specifically, with reduced generalized, but in some cases severe side effects
- Autoantigen-specific therapies are under investigation (oral tolerance induction), which are so far the most specific and least side effect-burdened approaches.

1. Introduction

Since uveitis is a disease that potentially destroys intraocular tissues, immediate antiinflammatory and causal treatment is needed in many cases. If uveitis is autoimmune mediated, immunosuppressive or immunomodulatory therapy is needed in those patients who do not sufficiently respond to corticosteroids. The use of corticosteroids is extensively discussed elsewhere in this issue.

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

The inflammation as well as relapses are orchestrated by T cells, which are an important target of immunosuppressive strategies. These therapies, however, also suppress necessary and desired immune responses to infections and tumors; therefore, more disease-specific therapies are preferred over generalized immunosuppression. Based on the increasing knowledge of the immune mechanisms that underlie autoimmune diseases, a new group of "biologicals" has been generated. These are immunologically active proteins focussing on specific cells, receptors or ligands. They target those immune responses that are involved in uveitis, either by blocking inflammatory cytokines (anti-TNF-therapies such as etanercept, infliximab or adalimumab), by

affecting T helper cells (anti-IL2 receptor) or suppressing the autoantigen-specific immune response by induction of mucosal tolerance (oral tolerance).
In the following new developments in immunosuppressive and immunomodulatory therapies will be described with respect to indication, immune mechanisms, effectiveness and side effects. It is important to keep in mind, that the use of most of the therapies described in this chapter is off–label, with the exception of cyclosporine. Nevertheless, there is a growing body of literature supporting the use of these substances for the treatment of uveitis.

Immunomodulatory substances

Anti-TNF-α treatment

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine, which is released primarily by activated monocytes and macrophages. It initiates the secretion of a cascade of other cytokines in many different cell types. Monocytes are activated to secrete IL-1 and -6, B cells produce antibodies and T cells IL-2, IFN-γ and other cytokines. In endothelial cells TNF-α upregulates different cytokines, adhesion molecules and inducible nitric oxide synthetase (iNOS). TNF-α has also effects on many non-immune cells. In the brain it induces fever and sleep, and in osteoblasts, fibroblast and myocytes the production of proteases, which will lead to tissue destruction. Besides the proinflammatory activity of TNF-α these latter effects are responsible for the destruction of bone and connective tissue in rheumatic diseases. In contrast, low concentrations of TNF-α have a neuroprotective function, inducing remyelination in the central and peripheral nervous system. This might be the reason for the demyelinating disease with MS-like symptoms or optic neuritis described as adverse event in some patients treated with anti-TNF-α therapies.
Nevertheless, therapeutics with inhibitory activity on TNF-α have been successfully applied in rheumatic disorders, however, the reports about effects on intraocular inflammatory diseases are controversial.
During the last years two substances have been used. Infliximab is a partially humanized monoclonal antibody neutralizing TNF-α by preventing its binding to both TNF-α receptors 1 and 2. A new completely humanized monoclonal antibody is now available, but there is at present no report about its effect in uveitis patients. Etanercept is a construct consisting of a TNF-α-receptor2 and a human IgG heavy chain, which acts as a receptor-agonist binding both, TNF-α and TNF-β. A new fusion protein with a TNF-receptor is currently under investigation for human use. Initial reports indicate a therapeutic effect in uveitis patients. Signaling through TNF receptor 2 is necessary for the induction of anterior chamber associated immune deviation (ACAID), an important feature to maintain the immune privilege of the eye. This was nicely demonstrated in a mouse model by Masli et al. and might explain the occurrence of uveitis in patients treated with etanercept for ankylosing spondylitis.

A major concern with the use of anti-TNF-α therapies is the development of autoantibodies in some patients even leading to symptoms of systemic lupus erythematodes.

Etanercept

Etanercept binds TNF-α as well as TNF-β preventing the interaction with the natural receptor on cell surfaces. Due to its long half live of 98 to 300 hours 25 mg of etanercept are applied subcutaneously two times a week only. Side effects include a local reaction at the injection site, which usually does not require special care. Other unwanted effects are a consequence of its antiinflammatory and immunosuppressive activity, which interferes with the host's defense against infections. These include respiratory infections, the reactivation of tuberculosis and sepsis, of which several of these patients have died. Since patients with rheumatoid diseases have an increased risk of infections due to their disease, close monitoring is mandatory.

In patients with chronic or relapsing uveitis etanercept was used with the aim to prevent relapses after disease has been controlled by methotrexate. With regard to the frequency of relapses and the final visual acuity, the authors did not find any significant difference between the treatment and placebo groups. Fortunately, no patient suffered from any irreversible long-term morbidity or mortality.

Reports about the efficacy of etanercept in children with treatment-resistant uveitis with or without underlying juvenile chronic arthritis are conflicting. Reiff et al. reported about alleviation of uveitis in 10 of 16 eyes and prevention of relapses in most of the children. Even after long-term follow up the authors noted a prolonged therapeutic effect. On the other hand, Smith et al. reported the results of a small, double-blind and placebo controlled trial of 12 children with pediatric uveitis treated with etanercept. They did not find any therapeutic effect in either group, questioning the efficacy of etanercept in these patients.

Infliximab

The monoclonal antibody infliximab is injected intravenously. The usual dose is 3 - 5 mg/kg body weight; escalation to 10 mg/kg is used in single cases. Infusions are repeated after 2 and 6 weeks and then every 8 weeks. Side effects during infusion include dizziness and headaches. Allergic reactions to infliximab seem to be rare. Similar to etanercept infliximab induces immunosuppression and thus inhibition of defense from infections. Viral and respiratory infections as well as tuberculosis occur frequently. Thus, before initiation of therapy tuberculosis has to be excluded by chest X-ray and tuberculin skin testing, In the case of positive results a prophylactic INH (isoniazid)-treatment is mandatory. Recently, infliximab has been associated with higher incidences of mortality and hospitalization of patients with moderate to severe congestive heart failure. Optic neuritis may develop but it seems that infliximab may also exert a direct toxic effect.

Infliximab has been used for the treatment of many different uveitis entities. In most of these studies patients with chronic or relapsing uveitis were included, who did not respond sufficiently to conventional therapy. Anterior uveitis associated with HLA-B27 seems to respond quickly to monotherapy with infliximab. Some of the patients experienced relapses after a median period of 5 months, which might reflect the natural course of the disease. Due to the severity of uveitis in Behçet's disease, several groups have used infliximab and published their results. A single infusion of infliximab rapidly induces a remission within one to two days and complete remission within two weeks. Retreatment of patients with relapses was successful, despite development of ocular and systemic tuberculosis in one patient, which responded to antituberculous treatment. The use of infliximab in children with Behçet's uveitis is limited, but shows positive effects.
Infliximab has been used more often than etanercept for the treatment of uveitis. Until now, there is no study directly comparing these two drugs. Only one single report of a patient whose Behçet´s disease did not respond to etanercept but subsequently to a single infusion with infliximab indicates that the monoclonal antibody might be superior to etanercept.

Interferon-α

Interferon-α and interferon-β (IFN-α, -β) are type 1 interferons, induced by viral infections and tumors or foreign cells. IFN- α subtypes are preferentially produced by monocytes/macrophages, but mainly by plasmacytoid dendritic cells (PDC) during viral infections, triggered by DNA with viral or bacterial CpG-motifs. It was thus primarily used for the treatment of chronic hepatitis B and C.
The mechanism of action of recombinant IFN-α2a treatment is not yet fully understood. The effect may include a modulation of the immune system. NK (natural killer) cells and NKT cells, a cell population bearing NK receptors as well as T cell receptors (of restricted variability) are stimulated with IFN-α. The original hypothesis was based on reports that the NK/NKT cell activity is impaired and their number decreased in several autoimmune animal models and human diabetes. NKT cells have an important regulatory function in the innate as well as the adaptive immune response. The deficiency of NK cells could be corrected with IFN-α treatment. Later, IFN-α was described as an inductor of circulating IL-1 receptor antagonists. In this case, induction of an anti-inflammatory status was suggested through modulation of the IL-1/IL-1receptor antagonist balance. Recent results suggest that host immunity is an important factor in the response to interferon therapy.
Side effects of IFN-α therapies are the development of anti-thyroid antibodies, sometimes leading to thyroiditis, and anti-DNA-antibodies. Since increased IFN-α production and anti-DNA antibodies are also found in patients with lupus erythematodes, it is a major concern that IFN-α-treatment even has the potential to induce SLE. Most patients experience flu-like symptoms, which resolve spontaneously.

In an uncontrolled prospective study 50 patients with Behçet´s disease and sight-threatening uveitis were treated with a daily subcutaneous dose of 6 million units recombinant human IFN-α2a. Forty-six patients responded well with increasing visual acuity and regressing intraocular inflammation. The overall activity of Behçet´s disease was reduced to 50 %, and after a mean observation period of 3 years 20 patients were able to discontinue treatment and were in remission for 7 to 58 months. The remaining patients could reduce their dose of IFN-α2a to 3 million units three times a week.

Daclizumab

T cells upregulate their receptor for IL-2 (IL-2R) upon activation. Targeting the α-chain of the high-affinity IL-2R will thus affect only activated T cells, the population that maintains the autoaggressive immune response, while leaving the pool of memory and naïve T cells untouched. In rodent experimental autoimmune uveitis the autoaggressive Th1 cells express large numbers of IL-2R. In a non-human primate model targeting IL-2 receptors could effectively downregulate experimentally induced intraocular inflammation, offering the rationale for treating the first patients in a nonrandomized open-label pilot study. Ten uveitis patients were successfully treated with the humanized antibody specific for the IL-2 receptor (daclizumab), 1 mg/kg bodyweight was infused in 2-week intervals. After 24 weeks the intervals between the infusions were increased to 4 weeks. Within the first year patients did not need any other immunosuppressive or antiinflammatory therapy besides daclizumab.
Meanwhile seven of these patients were followed for more than 4 years. During the 3 years follow up subcutaneous application of therapeutic antibody was tested (2 mg/kg bodyweight, 2 applications within the first 2 weeks, followed by 4 weekly maintenance treatments with 1 mg/kg body weight). In all patients treated s.c. the concomitant immunosuppressive therapy could be reduced, while visual acuity remained stable. Side effects within the first year of daclizumab therapy were granulomatous dermatitis in two patients, whereas during the following three years of treatment more side effects appeared, ranging from minor infections to renal cell carcinoma in one patient.

Oral tolerance induction

The various treatment strategies discussed above have one major feature in common: they generally suppress the immune system, but not only the autoaggressive immune response. Furthermore, the pharmaceutical and even some biological agents are burdened with severe side effects, which might even accumulate with duration of treatment. Although most of the side effects are dose dependent and can be reduced by combining different therapeutic agents, the side effects will limit efficiency of therapy in most patients, often resulting in loss of visual acuity for the sake of the patients' safety. It is therefore important to develop highly specific therapies, such as

the induction of antigen specific mucosal tolerance. In this case the antigen which is attacked by the immune system is applied orally, and in that manner induces regulatory cells downregulating the autoaggressive immune response.
This mechanism of mucosal tolerance is usually effective for nutritional proteins, preventing adverse reactions that potentially lead to food allergies. This tolerance is mediated by suppressor cells specific for the respective antigen; however, the exact mechanisms of this suppression are not yet fully elucidated. It is assumed that that suppressor T cells recognize the respective antigen and secrete suppressive cytokines, such as TGF-β, IL-10 (Th3, Tr type) or cytokines belonging to the respective antagonistic Th type of immune response. To date various antigens have been orally applied to uveitis patients.

Retinal autoantigens as tolerogens

In the first pilot study of oral tolerance induction two patients with chronic intermediate and Behçet's uveitis, respectively, both requiring permanent immunosuppressive therapy, were orally treated with retinal S-Ag. These patients received 30 mg of purified bovine retinal S-Ag, starting with 3 times a week initially. Later the intervals of oral antigen administration were extended and finally the patients were taken off oral S-Ag. In the 41 months follow up the disease activity decreased and as a positive effect of treatment with oral S-Ag, the conventional medication could be reduced.
Later a prospective, randomized, double blinded clinical phase I/II trial followed. Four groups of patients received either placebo, purified bovine retinal S-Ag, retinal extract enriched with S-Ag or bovine retinal extract to ensure that tolerance is enduced to all possible antigens, which might play a role in the course of uveitis. The read out in this study was the time from study entry to tapering off immunosuppressive therapy, and in the follow up the time until the next relapse occurred. With respect to both parameters, the patient group treated with purified oral S-Ag showed positive results compared to placebo controls or the other treatment groups. Unfortunately, the results did not reach statistical significance possibly due to a too small sample size.

HLA-peptide B27PD as oral tolerogen

The 14-mer peptide B27PD (ALNEDLSSWTAADT) has been shown to be highly effective for the treatment of experimental autoimmune uveitis in rats. Therefore a prospective uncontrolled open trial for 9 patients with chronic anterior, intermediate or posterior uveitis was initiated, using the encapsulated peptide for oral treatment. All patients were on long lasting conventional immunosuppressive therapy and either suffered from severe side effects or were unresponsive to this treatment. The patients received 4 mg of the peptide three times a week during the first 12 weeks and were then followed for another 9 months. The amount of concomitant immunosuppressive treatment was limited to 20 mg of prednisone or equivalent during the 12 weeks of tolerance induction, and during the whole study period conventional therapy was adjusted to the patients' disease activity.

In all patients, visual acuity and/or intraocular inflammation improved during the peptide treatment. This allowed reducing corticosteroid therapy in all patients within 2 - 6 weeks, resulting in an average steroid dose reduction from 10.4 mg (in the year prior to study entry) to 3.1 mg daily within the year after study entry. At the same time visual acuity increased slightly. Extensive in vitro testing of peripheral blood lymphocytes revealed that immune responses to mitogens (PHA, Phytohemagglutinin) and recall antigens (tetanus toxoid, PPD (purified protein derivative of M. tuberculosis) were not altered by peptide treatment, indicating that tolerance induction does not cause a generalized immunosuppression.
During the follow-up of 4 years, four patients were successfully retreated with oral peptide. The average visual acuity of all patients remained stable with reduced concomitant corticosteroid therapy.

Summary

- Uveitis patients with sight threatening chronic or remitting disease require immunosuppressive therapy if corticosteroids alone show unsatisfactory therapeutic effects or intolerable side effects.
- Immunosuppressive therapy with cytotoxic drugs (azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide or chlorambucil), antibiotics (sulfasalazine) or calcineurin inhibitors (cyclosporine A, tacrolimus) is usually combined with corticosteroids in order to save on the therapeutic dose of either drug and thus to reduce side effects. The therapeutic effect of conventional immunosuppressive agents may be delayed by several weeks or up to three months.
- New immunomodulatory therapies such as thalidomide, and biologicals targeting cytokines (anti-TNF-α: infliximab or TNF-αR-IgG: etanercept), cytokine receptors on immune cells (anti-IL-2Receptor: daclizumab) or the direct application of cytokines (IFN-α) are more specific in their mode of action. They have the potential to quickly induce remission in uveitis patients, even in those with certain underlying diseases (e.g. Behçet's disease). However, due to limited experience possible side effects are still not known.
- Immunological therapies with the capacity to re-induce tolerance to autoantigens without affecting other immune responses, like oral tolerance induction, are under investigation and have the potential to be void of adverse events.

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