Uveitis in patients with Multiple Sclerosis

An observational descriptive clinical study submitted in partial fulfillment of Master Degree in Ophthalmology

By

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List of Abbreviations

- **BSCVA**  Best spectacle corrected visual acuity
- **CADASIL**  Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
- **CF**  Counting fingers
- **CME**  Cystoid Macular Edema
- **CMV**  Cytomegalovirus
- **CNS**  Central Nervous System
- **DTPA**  Diethylene Triamine Pentaacetic Acid
- **EAE**  Experimental allergic encephalomyelitis
- **FFA**  Fundus Fluorescein Angiography
- **HHV-6**  Human herpesvirus 6
- **HLA**  Human Leucocytic Antigen
- **IFNβ**  Interferon beta
- **IOP**  Intra ocular pressure
- **I.V**  Intravenous
- **KPs**  Keratic Precipitates
- **MS**  Multiple sclerosis
- **OCT**  Optical Coherence Tomography
- **PML**  Progressive Multifocal Leucoencephalopathy
- **RAPD**  Relative afferent pupillary defect
- **SPECT**  Single Photon Emission Computed Tomography
- **SUN**  The Standardization of Uveitis Nomenclature
- **TDP**  Temporal disc pallor
- **VKH**  Vogt Koyanagy Harada disease
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Abstract

This is a cross sectional observational descriptive clinical study, in which 75 patients diagnosed with MS (of the Relapsing-Remitting type), according to McDonald criteria, underwent complete ophthalmological examination, in search for the presence, and type of uveitis. Patients having any other ocular disease or any history of ocular surgery or trauma in either eye, were excluded from our study.

From the 75 patients that were examined, we detected that eight eyes of 7 patients had intermediate uveitis. Five eyes had pars plana snowballs, and 3 eyes had vitreous cells. Those uveitic patients included 5 males and 2 females and had a mean age of 25.2 ±5.7 years.

The association between uveitis and MS was originally described by Rucker. The occurrence of this association varies widely, ranging from 0.4% to 26.9% in patients with MS and from 0.8% to 14% in patients with uveitis. A population-based study estimated the prevalence of uveitis in the general population at 52 cases per 100,000 person-years. In southern India, one in each 200 had uveitis in at least one eye not related to trauma or surgery. In the USA and Australia, a less than 1% prevalence of uveitis was found as well.

Key Words:

Cytomegalovirus – Intravenous - Multiple sclerosis
Uveitis is broadly defined as inflammation (ie, *itis*) of the uvea (from the Latin *uva*, meaning “grape”). Uveitis can be broadly categorized into infectious and non-infectious etiologies. Several uveitis classification schemes exist. These are based on anatomy (portion of the uvea involved: anterior, intermediate, posterior, and pan), clinical course (acute, chronic, and recurrent), etiology (infectious and noninfectious), and histopathology (granulomatous or non-granulomatous) (1).

Multiple Sclerosis (MS) is an inflammatory disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms (2). The name ‘*multiple sclerosis*’ refers to scars (scleroses—better known as plaques or lesions) particularly in the white matter of the brain and spinal cord. When myelin is lost, the axons can no longer effectively conduct signals (3).

Different types of uveitis (mainly intermediate uveitis, retinal periphlebitis and granulomatous irido-cyclitis) are associated with MS (4, 5,6,7). About 3-27% of patients with MS develop intermediate uveitis/pars planitis (8), and 7.8-14.8% of patients with intermediate uveitis/pars planitis develop MS (9). Most patients with MS-associated uveitis are white females between the ages of 20 and 50 years, and the diagnosis of MS precedes that of uveitis in 56% of cases, follows it in 25% and occurs concurrently in 19% (10). Moreover, uveitis was found to share common genetic susceptibility loci with different autoimmune diseases including MS (11).

The aim of the work is to study uveitis in a group of MS patients (of the relapsing-remitting type), in a trial to describe the relation and pattern of uveitis in Egyptian MS patients.
**Uveitis**

The uvea consists of the middle, pigmented, vascular structure of the eye and includes the iris, ciliary body, and the choroid. Uveitis is broadly defined as inflammation (i.e., *itis*) of the uvea. Uveitis can be broadly categorized into infectious and non-infectious etiologies (1).

Several uveitis classification schemes exist. The Standardization of Uveitis Nomenclature (SUN) Working Group, in 2005, developed an anatomical classification system, descriptors, standardized grading systems, and terminology to use for following the activity of uveitis. This system was adopted by leading specialists from all over the world (12). (Tables 1, 2, and 3)

Table 1: The SUN Working Group Anatomical Classification of Uveitis

<table>
<thead>
<tr>
<th>Type</th>
<th>Primary Site of Inflammation</th>
<th>Includes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior Uveitis</td>
<td>Anterior chamber</td>
<td>Iritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iridocyclitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anterior cyclitis</td>
</tr>
<tr>
<td>Intermediate Uveitis</td>
<td>Vitreous</td>
<td>Pars planitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posterior cyclitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyalitis</td>
</tr>
<tr>
<td>Posterior Uveitis</td>
<td>Retina or choroid</td>
<td>Focal, multifocal, or diffuse choroiditis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chorioretinitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retinochoroiditis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retinitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuroretinitis</td>
</tr>
<tr>
<td>Panuveitis</td>
<td>Anterior chamber, vitreous,</td>
<td>Anterior chamber, vitreous, and retina</td>
</tr>
<tr>
<td></td>
<td>and retina or choroid</td>
<td>choroid</td>
</tr>
</tbody>
</table>
## Table 2: The SUN Group Descriptors in Uveitis

<table>
<thead>
<tr>
<th>Category</th>
<th>Descriptor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Sudden</td>
<td>--------</td>
</tr>
<tr>
<td></td>
<td>Insidious</td>
<td>--------</td>
</tr>
<tr>
<td>Duration</td>
<td>Limited</td>
<td>≤3 months’ duration</td>
</tr>
<tr>
<td></td>
<td>Persistent</td>
<td>&gt;3 months’ duration</td>
</tr>
<tr>
<td>Course</td>
<td>Acute</td>
<td>Episode characterized by sudden onset and limited duration.</td>
</tr>
<tr>
<td></td>
<td>Recurrent</td>
<td>Repeated episodes separated by periods of inactivity without treatment ≥3 months’ duration.</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>Persistent uveitis with relapse in &lt;3 months after discontinuing treatment.</td>
</tr>
</tbody>
</table>

## Table 3: The SUN Working Group Activity of Uveitis Terminology

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive</td>
<td>Grade 0 cells (anterior chamber)</td>
</tr>
<tr>
<td>Worsening activity</td>
<td>2-step increase in level of</td>
</tr>
<tr>
<td>Stage</td>
<td>Description</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Inflammation</td>
<td>inflammation (eg. anterior chamber cells, vitreous haze) or increase from grade 3+ to 4</td>
</tr>
<tr>
<td>Improved activity</td>
<td>2-step decrease in level of inflammation (eg. anterior chamber cells, vitreous haze) or decrease to grade 0</td>
</tr>
<tr>
<td>Remission</td>
<td>Inactive disease for ≥3 months after discontinuing all treatments for eye disease</td>
</tr>
</tbody>
</table>

**Anterior Uveitis:**

Anterior uveitis is the most common form of uveitis. According to the SUN classification system, the anterior chamber is the primary site of inflammation in anterior uveitis. Anterior uveitis can have a range of presentations, from a quiet eye with low grade inflammatory reaction apparent only on close examination to a painful red eye with moderate to severe inflammation. Inflammation confined to the anterior chamber is called ‘iritis’; if it spills over into the retrolental space, it is called ‘iridocyclitis’; if it involves the cornea, it is called ‘keratouveitis’; and if the inflammatory reaction involves the sclera and uveal tract, it is called ‘sclerouveitis’.

By far, most types of anterior uveitis are sterile inflammatory reactions, whereas many of the posterior uveitic syndromes are infectious in origin. In contrast to endophthalmitis from an infectious source, only 2
noninfectious causes (typically the diseases associated with HLA-B27 and Adamantides-Becheet syndrome) are associated with hypopyon.

**Intermediate Uveitis:**

The SUN working group defines intermediate uveitis as that in which the major site of inflammation is the vitreous. Intermediate uveitis accounts for up to 15% of all cases of uveitis. It is characterized by ocular inflammation concentrated in the anterior vitreous and the vitreous base overlying the ciliarybody and peripheral retina-pars plana complex. Inflammatory cells may aggregate in the vitreous (snow balls), where some coalesce. In some patients, inflammatory exudative accumulation on the inferior pars plana (snowbaking) seems to correlate with a more severe disease process. There may be associated retinal phlebitis. Anterior chamber reaction may occur as a spillover from the vitreous. Inflammation of the middle portion (posterior ciliary body, pars plana) of the eye manifests primarily as floaters affecting vision. Diseases associated with intermediate uveitis include MS, Sarcoidosis, Lyme disease, Peripheral toxocariasis, Syphilis, Tuberculosis, Primary Sjogren Syndrome, Intraocular lymphoma and Pars planitis.

The term *pars planitis* refers to the subset of intermediate uveitis where there is snowbank or snowball formation in the absence of an associated infection or systemic disease; it is the most common form of intermediate uveitis. Its pathogenesis is not well understood but is thought to involve autoimmune reactions against the vitreous, peripheral retina, and ciliary body. *An association with the HLA-DR15 and pars planitis has been found. HLA-DR15 is also associated with M.S,*
suggesting a common immunogenetic predisposition to both diseases (13).

**Posterior Uveitis:**

Posterior Uveitis is defined by the SUN classification system as intraocular inflammation primarily involving the retina and/or choroid. Inflammatory cells may be observed diffusely throughout the vitreous cavity, overlying foci of active inflammation, or on the posterior vitreous face. Macular edema, retina vasculitis, and retinal or choroidal neovascularization, although not infrequent structural complications of certain uveitic entities, are not considered essential to the anatomical classification of posterior uveitis (14).

Diseases associated with posterior uveitis include Collagen Vascular Diseases (e.g Systemic lupus erythematosus, Polyarteitis nodosa and Wegener granulomatosis) and Inflammatory Chorio-retinopathies of Unknown Etiology (or White Dot Syndromes) which are a heterogenous group of inflammatory disorders with overlapping clinical features that share the common presence of discrete, multiple, well-circumscribed yellow-white lesions at the level of the retina, outer retina, RPE, choriocapillaris, and choroid during some phase of their disease course, they include Birdshot retino-choroidopathy, Acute posterior multifocal placoid pigment epitheliopathy, Serpigenous Choroditis, Multifocal choroiditis and panuveitis, Punctate inner choroidopathy, Subretinal fibrosis and uveitis syndrome, Multiple evanescent white dot syndrome, Acute retinal pigment epithelitis, and Acute zonal occult outer retinopathy (14).
**Panuveitis:**

The designation ‘panuveitis’ or ‘diffuse uveitis’, by definition, requires involvement of all anatomical compartments of the eye—namely, the anterior chamber, vitreous, retina and/or choroid—with no single predominant site of inflammation. Generally, panuveitis is bilateral, although 1 eye may precede, and the severity is not necessarily symmetric (15).

Diseases associated with panuveitis maybe infectious or non-infectious. Non-infectious causes include Sarcoidosis, Sympathetic Ophthalmia, Vogt-Koyanagi-Harada Disease (VKH), and Adamantiades-Behcet Disease.

**Infectious Uveitis:**

Viruses, fungi, protozoa, helminthes, and bacteria can all cause infectious uveitis. Each organism can produce inflammation in a different part of the uveal tract. Some agents, such as herpes simplex virus, may cause anterior and/or posterior uveitis. Others, such as syphilis, lyme borreliosis, and onchocerciasis, usually cause panuveitis.

**Symptoms of Uveitis:**

Symptoms produced by uveitis depend on which part of the uveal tract is inflamed, the rapidity of onset (sudden or insidious), the duration of the disease (limited or persistent), and the course of the disease (acute, recurrent, or chronic).
Acute-onset anterior uveitis (iridocyclitis) causes pain, photophobia, redness, and blurred vision. In contrast, chronic iridocyclitis in patients with JRA/JIA (Juvenile Rheumatoid Arthritis/ Juvenile Idiopathic Arthritis) may not be associated with any symptoms at all. However, with chronic iridocyclitis, blurred vision may develop as a result of calcific band keratopathy, cataract, or cystoid macular edema (CME). Recurrent anterior uveitis is marked by periods of inactivity of 3 or more months off medications followed by a return of symptoms.

Intermediate uveitis produces symptoms of floaters and blurred vision. Floaters result from the shadows cast by vitreous cells and snowballs on the retina. Blurred vision may be due to CME or vitreous opacities in the visual axis.

Presenting symptoms in patients with posterior uveitis include painless decreased visual acuity, floaters, photopsia, metamorphopsia, scotomata, or a combination of these. This blurred vision may be due to the primary effects of uveitis such as retinitis and /or choroiditis directly affecting macular function or to the complications of inflammation such as CME, epiretinal membrane, retinal ischemia, and choroidal neovascularization. Blurred vision may also result from refractive error such as a myopic or hyperopic shift associated with macular edema, hypotony, or a change in lens position. Other possible causes of blurred vision include opacities in the visual axis from inflammatory cells, fibrin, or protein in the anterior chamber, keratic precipitates (KPs), complicated cataract, vitreous debris, macular edema, and retinal atrophy.

Pain of uveitis usually results from the acute onset of inflammation in the region of the iris, as in acute iritis, or from secondary glaucoma. The pain associated with ciliary spasm in iritis may be a referred pain that
seems to radiate over the larger area served by cranial nerve V (trigeminal nerve). Epiphora and photophobia are usually present when inflammation involves the iris, cornea, or ciliary body. Occasionally, uveitis is discovered on a routine ophthalmic examination in an asymptomatic patient (16).

**Signs of Uveitis:**

*Anterior segment*

Signs of uveitis in the anterior portion of the eye include

- KPs
- Cells
- Flare
- Hypopyon
- Pigment dispersion
- Pupillary miosis
- Iris nodules
- Synechiae (both anterior and posterior)
- Band keratopathy (seen with long-standing uveitis)

*Keratic precipitates* are collections of inflammatory cells on the corneal endothelium. When newly formed they tend to be white and smoothly rounded, but they then become crenated (shrunken), pigmented,
or glassy. Large, yellowish KPs are described as ‘mutton-fat’ KPs; these are usually associated with granulomatous types of inflammation.

Perilimbal vascular engorgement (ciliary flush) or diffuse injection of the conjunctiva, episclera, or both is typical with acute anterior uveitis. With increased capillary permeability, the anterior chamber reaction can be described as:

- **Serous** (aqueous flare caused by protein influx).
- **Purulent** (polymorphonuclear leukocytes and necrotic debris causing hypopyon).
- **Fibrinous** (plasmoid or intense fibrinous exudate).
- **Sanguinoid** (inflammatory cells with erythrocytes manifested by hypopyon mixed with hyphema).

The SUN group developed an updated method of grading anterior chamber cells and flare. The intensity of the cellular reaction in the anterior chamber is graded according to the number of inflammatory cells seen in 1x1mm high-powered beam at full intensity at a 45º-60º angle (Table 4).

Flare may also be graded similarly, and the SUN group described flare intensity as it had been described previously by Hogan and Kimura (Table 5) (17).
Table 4: The SUN Working Group Grading Scheme for Anterior Chamber Cells.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cells in field (high-intensity 1x1mm slit beam)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5+</td>
<td>1-5</td>
</tr>
<tr>
<td>1+</td>
<td>6-15</td>
</tr>
<tr>
<td>2+</td>
<td>16-25</td>
</tr>
<tr>
<td>3+</td>
<td>26-50</td>
</tr>
<tr>
<td>4+</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

Table 5: The SUN Working Group Grading System for Anterior Chamber Flare.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1+</td>
<td>Faint</td>
</tr>
<tr>
<td>2+</td>
<td>Moderate (iris and lens details clear)</td>
</tr>
<tr>
<td>3+</td>
<td>Marked (iris and lens details hazy)</td>
</tr>
<tr>
<td>4+</td>
<td>Intense (fibrin or plasmoid aqueous)</td>
</tr>
</tbody>
</table>
Iris involvement may manifest as either anterior or posterior synechiae, iris nodules (Kooppe nodules at the pupillary border, Busacca nodules within iris stroma, and Berlin nodules in the angle), iris granulomas, heterochromia (eg, Fuchs heterochromic iridocyclitis) or stromal atrophy (eg, herpetic uveitis).

*Intermediate segment:*

Signs in the intermediate anatomical area of the eye include:

- Vitreal inflammatory cells, which are graded from 0 to 4+ in density. (Table 6)
- Snowball opacities, which are common with intermediate uveitis.
- Snowbanking, which are exudates over the pars plana.
- Vitreal strands.

**Table 6: Grading of vitreal inflammatory cells**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number of cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No cells</td>
</tr>
<tr>
<td>0.5+</td>
<td>1-10</td>
</tr>
<tr>
<td>1+</td>
<td>10-20</td>
</tr>
<tr>
<td>2+</td>
<td>20-30</td>
</tr>
<tr>
<td>3+</td>
<td>30-100</td>
</tr>
<tr>
<td>4+</td>
<td>&gt; 100</td>
</tr>
</tbody>
</table>