

## REVIEW

# Diseases of the Eye with Systemic Involvement and/or Acute Presentation

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**KEY WORDS:** *optic neuritis; multiple sclerosis; age-related macular degeneration; diabetic retinopathy; glaucoma; uveitis*

#### ABBREVIATIONS

AGEs = advanced end glycation products;  
AMD = age-related macular degeneration;  
DR = diabetic retinopathy;  
FDA = Food & Drug Administration (Agency);  
MRI = magnetic resonance imaging;  
MS = multiple sclerosis;  
NMO = neuromyelitis optica;  
RPE = retinal pigment epithelium;  
VEGF = vascular endothelial growth factor

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*Manuscript received November 15, 2012;*

*Revised manuscript received June 1, 2013;*

*Accepted June 15, 2013*

#### ABSTRACT

Optic neuritis is defined as an inflammation of the optic nerve, which is mostly idiopathic. However, it can be associated with variable causes: demyelinating lesions, autoimmune disorders, infections, compressive, toxic, metabolic and hereditary conditions. It is divided into arteritic, which is commonly seen in temporal arteritis/poly-myalgia rheumatica and non-arteritic optic neuritis, which is associated with advanced age, atherosclerosis, hypertension and hyperlipidemia. Among demyelinating disorders, multiple sclerosis is the most common cause. The term optic neuritis is indicated by sub-acute unilateral painful visual loss mostly in a young healthy female and by excluding glaucoma. The clinical diagnosis of optic neuritis consists of the classic triad of visual loss, periocular pain and dyschromatopsia which requires careful ophthalmic, neurologic and systemic examinations to distinguish between typical and atypical optic neuritis. In neuromyelitis optica, optic neuritis is initially misdiagnosed as optic neuritis in multiple sclerosis or other conditions such as ischemic optic neuritis and Leber's disease. Therefore, differential diagnosis is necessary to make a proper treatment plan. According to Optic Neuritis Treatment Trial, the first line of treatment is intravenous methylprednisolone with faster recovery and less chance of recurrence of optic neuritis and conversion to multiple sclerosis.

Apart from optic neuritis of various causes, loss of vision could be due to glaucoma or uveitis. Glaucoma is optic nerve damage due to an interruption of the production and/or abduction of vitreous gel of the eye. Uveitis refers to a group of heterogeneous diseases that share the features of intraocular inflammation, but whose etiologies include idiopathic autoimmune disease, infections and masquerade syndromes. Acute retinal necrosis and detachment may have a debilitating effect on vision and must be rapidly diagnosed and managed. The above-mentioned clinical entities, their etiologies and current therapies are briefly discussed in this review.

#### INTRODUCTION

The internist is often called upon to render opinion and evaluate patients who present with ocular problems and/or systemic diseases with ocular involvement. The internist is also the initial physician providing treatment for these conditions, and therefore a working knowledge of the eye examination is essential in clinical practice. During this initial evaluation, a decision will be made for subsequent referral to an ophthalmologist. It is important to determine which patients will need urgent ophthalmology referral

to prevent loss of vision, or when it would be safe to initiate treatment in the office and defer ophthalmology referral. To make this judgment one needs to seek the presence of alarming symptoms and signs. If such signs are elicited, then an urgent referral to ophthalmology is indicated. An overview of the most common ocular problems an internist may encounter will be herein presented and discussed (Table 1).

**TABLE 1. Diseases of the Eye with Systemic Involvement**

<b>Connective Tissue Diseases</b>
Systemic Lupus Erythematosus
Rheumatoid arthritis
Sjogren's Syndrome
Mixed Connective Tissue Disease
Reiter's Syndrome
Vasculitides
Behcet's Syndrome
Giant-cell-Arteritis-Polymyalgia Rheumatica
Wegener's Disease
Granulomatous Diseases
Sarcoidosis
Crohn's Disease
Ulcerative Colitis
Infectious Diseases
Tuberculosis
Lyme Disease
Syphilis
Whipple's Disease
Leptospirosis
HIV
HSV-VZV-CMV
Cysticercosis
Toxocariasis
Candida spp
Aspergillus spp
Mucor
Neurologic Diseases
Multiple Sclerosis
Neuromyelitis optica
Hereditary Diseases
Vogt-Koyanagi-Harada
Wilson's Disease
Other
Diabetes Mellitus
Leukemias-Lymphomas
Amyloidosis

CMV = cytomegalovirus; HIV = human immunodeficiency virus; HSV = herpes simplex virus; VZV = varicella zoster virus

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**OPTIC NEURITIS**

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Optic neuritis is a clinical entity that presents with eye pain and blurred vision. Based on its etiology, it can be divided into arteritic, and non-arteritic optic neuritis, compressive, demyelinating, toxic, metabolic and hereditary optic neuritis. Arteritic optic neuritis is associated with connective tissue diseases, whereas non-arteritic is related to atherosclerosis, hypertension, diabetes and hyperlipidemia. Compressive optic neuritis is due to compression of the optic nerve, e.g. by tumors, aneurysms, etc. Toxic optic neuritis is the result of damage to the optic nerve by chemical substances like drugs, alcohol and cigarette smoking. Metabolic optic neuritis associated with diabetes mellitus and hereditary optic neuritis comprises an extremely rarely seen entity.<sup>1,2</sup>

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**ARTERITIC OPTIC NEURITIS**

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It is usually seen among patients with temporal (or giant-cell) arteritis and/or polymyalgia rheumatica, as these two entities are closely related conditions, affecting middle-aged or older people. Many authorities consider them to be different stages of the same disease.<sup>3</sup> Polymyalgia rheumatica is an inflammatory condition of unknown cause characterized by aching and morning stiffness in the cervical region and shoulder and pelvic girdles. It usually responds rapidly to low doses of corticosteroids and has a favorable prognosis. The onset of giant-cell arteritis is usually insidious, but may sometimes be abrupt, with partial or complete loss of vision in one or rarely both eyes, as its first manifestation.<sup>4</sup> Giant-cell arteritis presents with fever and fatigue due to anemia in about 50% of the patients, whereas temporal lobe headache is present in over 2/3 of the patients.<sup>5</sup> Among individuals > 65 years old, giant-cell arteritis is responsible for > 15% of cases of fever of unknown origin.<sup>6,7</sup> Patients may have jaw claudication, proximal myalgia and arthralgia, scalp tenderness, headache, fatigue, and a significantly increased erythrocyte sedimentation rate and C-reactive protein level. Amaurosis fugax is a threatening sign of impending arteritic optic neuritis.<sup>6</sup> As compared to non-arteritic, the vision loss is more severe and the optic disc is pale. For diagnosing giant-cell arteritis, the American College of Rheumatologists has established the following criteria:

- Age at onset  $\geq$  50 years old
- New headache
- Temporal artery with tenderness in palpation or decreased pulsation, unrelated to atherosclerosis
- Biopsy compatible with giant-cell arteritis
- Increased ESR ( $\geq$  50 mm/h)

If three of the above-mentioned five criteria are fulfilled, then the diagnosis of giant-cell arteritis is made.<sup>8</sup> Rarely, can

arteritic optic neuritis occur in other connective tissue disorders, such as sarcoidosis and Wegener's granulomatosis.

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### NON-ARTERITIC OPTIC NEURITIS

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It is more common than arteritic neuritis and is associated with age, atherosclerosis, hypertension, diabetes mellitus and hyperlipidemia. Its main categories are age-related macular degeneration (AMD) and diabetic retinopathy (DR) resulting in macular edema.

**Age-related Macular Degeneration (AMD).** Age-related macular degeneration is the most common cause of blindness in individuals over the age of 55 years in the developed world.<sup>9</sup> Its prevalence is estimated to be 0-2% in those aged 55 to 64 years and increases to 13% in those older than 85 years.<sup>10</sup> The disease in its early stages develops slowly and asymptotically over a number of years.<sup>11</sup> In this disease, the photoreceptors of the macula (the central retina) become damaged and die.<sup>12</sup> AMD results in central vision loss and is responsible for one-third of all forms of untreatable loss of vision.<sup>13</sup> An estimated 9 million older Americans have some form of AMD, and about 1.75 million have advanced AMD.<sup>14,15</sup> AMD is a disease of the elderly, and evidence suggests that 10% of individuals aged 65 to 74 years and 30% of those aged 75 to 85 years have evidence of AMD.<sup>16</sup> AMD is a gradual, painless, irreversible process in which the patient loses bilateral vision.<sup>17</sup>

Age is the strongest risk factor for AMD. Apart from age, cigarette smoking, with a direct association of the number of cigarettes with the risk of developing AMD.<sup>18,19</sup> Genetic factors are responsible for up to 23% of cases, whereas complement factor H is also implicated.<sup>20-22</sup>

AMD starts with deposits of lipid material that accumulate under the retinal pigment epithelium (RPE). These deposits, which appear as pale yellow spots on the retina, are called *drusen*.<sup>21</sup> With increasing age, the RPE cells, which form the blood-retinal barrier, become less efficient and the retina is no longer able to receive the proper nutrition. This decline in the efficiency of the RPE cells also results in the accumulation of waste products (drusen).<sup>21</sup> However, most people with evidence of drusen deposits maintain good vision.

Regarding therapeutical measures, laser photocoagulation in AMD and photodynamic therapy with verteporfin showed a significant reduction in moderate visual loss among patients with classic choroidal neovascularization.<sup>23</sup> Inhibitors of vascular endothelial growth factor (VEGF) have been used with good results, but there are some adverse effects like endophthalmitis, injury to the lens and retinal detachment.<sup>23</sup> Stem-cell therapy is now being tested to regenerate damaged retinal cells.<sup>24</sup>

**Diabetic retinopathy (DR).** Diabetic retinopathy (DR) is characterized by the progressive development of well-defined morphological abnormalities in the retinal microvasculature

that can remain relatively stable, that is non-proliferative DR or progress to diabetic macular edema and/or proliferative DR.<sup>25,26</sup> DR is one of the most common complications of diabetes and is a leading cause of blindness in people of working age in industrialized countries.<sup>27,28</sup> Approximately 25% of patients with Type 1 diabetes may have signs of retinopathy after 5 years of diabetes, increasing to 60% after 10 years.<sup>29</sup> After 25 years, almost all (97%) Type 1 diabetics will develop retinopathy.<sup>30</sup> Type 2 diabetic patients may already have background retinopathy at the time of diagnosis and over 60% will develop some form of retinopathy after 20 years.<sup>31</sup> The number of patients with DR was 5.8 million in 2005. However, this number will triple to 17.7 million in 2050.<sup>32</sup> With changes in lifestyle and increases in lifespan along with the global prevalence of diabetes, it is expected that DR will have a continuously growing impact.

The progression of DR follows a pattern characteristic of ischemic retinopathy.<sup>33</sup> In the beginning, vascular alterations include changes in blood flow, death of retinal pericytes, basement membrane thickening and subtle increases in vascular permeability. As the disease progresses, obvious alterations in the vascular structure can be seen upon ophthalmoscopic examination. These include non-perfused vessels, microaneurysms, dot/blot hemorrhages, cotton-wool spots, venous beading, vascular loops and significant vascular leakage. In many patients, the retinopathy progresses to proliferative DR, in which the new vessel walls are weak and allow the blood to leak out of the vessels, resulting in vitreous hemorrhage and subsequent retinal detachment. The mechanisms by which elevated blood glucose causes tissue injury and disease progression in the retina are not fully understood. However, studies have demonstrated that DR is a multifactorial disease involving multiple pathways, including aldose reductase pathway, oxidative stress, activation of protein kinase C and formation of advanced glycation end products (AGEs). These pathways lead to retinal pathological changes by causing osmotic vascular damage, inducing cell dysfunction and apoptosis through activation of mitogen-activated protein kinases (MAPKs) and oxidation of intracellular components, inducing production of angiogenic cytokines and breakdown of the vascular junction proteins.<sup>34-38</sup> One of the major hallmarks of DR is increased vascular permeability, which leads to the development of retinal hemorrhages and fluid accumulation in the macula, which is referred to as diabetic macular edema.<sup>39</sup>

Since the last two decades there have been significant developments in the emerging field of pharmacotherapy of DR. The advent of laser photocoagulation three decades back, was really useful in limiting vision loss in most of the cases and is still considered gold standard therapy for the treatment of DR. However, corticosteroids and anti-VEGF agents have shown promising results with regard to prevention of neo-vascularisation, but remained limited in use due to their short-duration effects. Additionally, none of these agents have been able to substitute the remarkable durability and effectiveness of pan-retinal photocoagulation.

Studies have led to the recognition of hyperglycemia, hypertension and dyslipidemia as major risk factors for DR. Consequently, tight glycemic control, blood pressure control and lipid-lowering therapy have all shown proven benefits in reducing the incidence and progression of DR.<sup>39-41</sup> Fenofibrate has been shown to reduce the frequency of first laser treatment for macular edema by 31% and for proliferative retinopathy by 30%.<sup>42</sup> The protein kinase C inhibitor ruboxistaurin mesilate, administered orally was effective in halting diabetic macular edema and vision loss, but not in preventing progression of diabetic retinopathy.<sup>43</sup> Laser photocoagulation and vitrectomy remain as the two conventional approaches for treating sight-threatening conditions such as macular edema and proliferative DR. Anti-VEGF therapy represents a recent breakthrough as clinical trials have demonstrated beneficial effects of VEGF blockers (pegaptanib, ranibizumab and bevacizumab) in reducing macular edema and causing neo-vascular regression, particularly when combined with laser photocoagulation.<sup>44</sup> In spite of this progress, DR remains a major clinical challenge and the number of patients keeps growing as it is sometimes difficult to achieve tight glycemic control throughout the course of the disease. Moreover, DR can develop even after tight control is initiated due to a phenomenon termed 'metabolic memory' in which the retinal endothelial cells manifest high-glucose-induced biochemical alterations long after the initial insult.<sup>45</sup> Laser photocoagulation and anti-VEGF therapy are not always effective and anti-VEGF therapy requires repeated treatment and may impair neuronal and vascular survival function.<sup>46-48</sup> Thus, there is a great need for developing new therapeutic approaches for this devastating disease. Vitrase (hyaluronidase ovine) is the first and only pure, preservative-free, thimerosal-free, ovine hyaluronidase, which is FDA-approved as a spreading agent. Intravitreal vitrase has shown efficacy and safety in a Phase III clinical trial to investigate its promotion of the clearance of vitreous hemorrhage from proliferative DR, although the agent is not FDA-approved for this purpose.<sup>49,50</sup>

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#### CENTRAL RETINAL ARTERY OCCLUSION

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Central retinal artery occlusion is usually caused by embolism from atherosclerotic plaques or cardiac thrombi or endocarditis of the central retinal artery and produces sudden painless blindness or visual field deficit. Immediate treatment is warranted as beyond 72 hours of the occlusion, it is very unlikely that increased perfusion will improve vision.

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#### CENTRAL RETINAL VEIN OCCLUSION

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It occurs mainly in elderly patients with diabetes mellitus, hypertension, among patients with glaucoma and in cases of increased blood viscosity due to other reasons (e.g. Behçet's

disease). It manifests as sudden painless loss of vision. In patients in whom normal retinal perfusion is re-established normalization of vision may recur.

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#### RETINAL DETACHMENT

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Retinal necrosis may lead to retinal detachment, which is the separation of the neural retinal layer from the underlying retinal pigment epithelium layer. It is painless and starts with flashes of light, floaters and blurred vision that may progress to a curtain falling down. Treatment includes corticosteroids, laser, diathermy or cryotherapy, photocoagulation, or intravitreal surgery depending on the location and the extent of the detachment.<sup>51</sup>

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#### DEMYELINATING OPTIC NEURITIS

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Demyelinating optic neuritis is an inflammatory process of the optic nerve occurring most commonly in the 18-to 45-year-old age group. It is often idiopathic (50% of cases), but it is commonly associated with neuro-inflammatory diseases (e.g., multiple sclerosis, neuromyelitis optica). Common presenting symptoms include rapidly progressive onset of blurred vision, decreased color vision and ocular pain worse with eye movement. Patients may also complain of abnormal sensation associated with objects moving back and forth (Pulfrich phenomenon) and may have worsening symptoms with an increase in body temperature (Uhthoff's phenomenon). Optic neuritis in multiple sclerosis (MS), a demyelinating disease that usually affects young people (<45 years old), especially women, manifests with sudden blurred vision, which deteriorates within 5 to 8 days, is usually unilateral and characteristically there is pain in the eye or around it that gets worse with eye movements. This optic deterioration may become better within a six months period. Recurrence of optic neuritis is common.<sup>52</sup>

Examination of patients with typical demyelinating optic neuritis may reveal a relative afferent pupillary defect in unilateral or asymmetric cases, decreased color vision and visual field defects. Optic nerve head swelling is seen at the onset of symptoms in roughly 33% of patients, with a normal-appearing disc in 66% of patients. Magnetic resonance imaging (MRI) with contrast and fat suppression is the modality of choice for identifying optic nerve inflammation, as well as other inflammatory lesions, vascular lesions and tumors. Cerebrospinal fluid may also be helpful diagnostically, especially in atypical cases or when neuro-inflammatory disease or central nervous system infection is suspected.<sup>53</sup> Although patients may have associated white matter brain lesions with idiopathic disease, they are at significantly higher risk for multiple sclerosis if there are multiple, ovoid white matter lesions, particularly in the region of the corpus callosum. It is estimated that patients

who present with optic neuritis and without findings in MRI have 16% probability to develop multiple sclerosis within 5 years, whereas patients who have abnormal MRI findings on first episode, consist 50% of all cases and have substantially bigger probability of developing multiple sclerosis within 5 to 10 years.<sup>54,55</sup>

The Optic Neuritis Treatment Trial demonstrated that treatment with intravenous (IV) steroids hastens visual recovery, although there is no significant improvement in final visual outcome. Treatment with oral steroids, however, may increase the risk of recurrence and the risk of progression to multiple sclerosis, so it is generally avoided. Treatment typically consists of methylprednisolone 1 g/day IV for 3 days followed by an oral prednisone tapering.

Neuromyelitis optica (NMO) is an acute inflammatory demyelinating disease mainly involving the optic nerves and spinal cord. Optic neuritis in NMO and MS are nearly identical in their initial presentation. However, demyelinating NMO is more violent and devastating than MS, hence its correct diagnosis is very important. In more than 85% of patients with NMO, attack recurs in the form of optic neuritis, transverse myelitis, or both, resulting in around 50% of cases in paralysis or blindness within 5 years. Sometimes patients with transverse myelitis in the cervical spine experience respiratory failure and even death.<sup>55,56</sup>

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#### TOXIC OPTIC NEURITIS

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Toxins closely associated with optic neuropathy include carbon monoxide, ethylene glycol, perchloroethylene, methanol and tobacco. Drugs associated with optic neuropathy are ethambutol, clioquinol, isoniazid, amiodarone, linezolid, methotrexate, sildenafil, oxymetazoline, and infliximab. Moreover, various chemotherapeutic agents are identified to cause optic atrophy, including vincristine, cisplatin, carboplatin and paclitaxel. Nutritional deficiencies such as vitamin B12 in poor countries have a significant role in the endemic optic neuropathy which deteriorates by tobacco use.<sup>53,55</sup>

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#### HEREDITARY OPTIC NEURITIS

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Leber's Hereditary Optic Neuropathy involves sub-acute and painless visual loss with central scotoma and poor color vision with sequential involvement of both eyes over a period of weeks to months. This disorder predominantly affects young men (80%–90%) and is inherited from maternal mitochondrial DNA. Funduscopy examination mainly shows circumpapillary telangiectasia, while about 1/3 of patients primarily have a normal disc appearance. Fat suppressed orbital MRI usually shows enhancement of the optic nerve.<sup>55</sup>

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#### COMPRESSIVE OPTIC NEURITIS

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Compressive optic neuropathies may be caused by sinus mucocoeles, arterial aneurysm, tumors, mass lesions, thyroid eye disease or other orbital processes. Brain and orbital MRI confirms or exclude diagnoses of compressive optic neuropathy.<sup>55</sup>

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#### GLAUCOMA

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Glaucoma is the leading cause of vision loss and irreversible blindness worldwide. In most patients with glaucoma, loss of vision is insidious and usually painless. However, early detection and treatment of glaucoma is recognized as beneficial in arresting or retarding glaucoma.<sup>57</sup> Consequently, guidelines have been drawn up to improve the care and outcome of patients with glaucoma. Glaucoma is associated with optic nerve damage due to an interruption in the production and/or abduction of vitreous gel of the eye.

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#### UVEITIS

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Uveitis refers to a group of heterogeneous diseases that share the features of intraocular inflammation but whose etiologies include idiopathic autoimmune disease, infections, rheumatologic diseases and masquerade syndromes. Correct diagnosis with timely and appropriate therapy is the key to reducing disease-associated morbidity. The multitude of possible causes can create diagnostic challenges, but a successful approach includes a targeted history of the illness and associated symptoms, detailed ocular evaluation and specific laboratory investigations.<sup>58</sup>

Uveitis can refer to inflammation of one or all three components, may also include primary inflammations of the retina and vitreous, and is often found in connection with systemic disease. The most critical question in evaluating a patient with intraocular inflammation is whether the disease can be classified into a specific, defined syndrome. If the answer is yes, then the treatment path is clarified. If the specific syndrome is elusive, one must take the appropriate steps to try to define the underlying pathophysiology, whether it is autoimmune, infectious, neoplastic or other masquerade syndromes, as the appropriate treatment for these types of diseases vary widely.<sup>59</sup>

Proper classification according to guidelines is critical for the development of a differential diagnosis for the etiology of uveitis in affected patients. The anatomic compartment is determined by the primary site of the inflammation: anterior (anterior chamber), intermediate (vitreous), posterior (retina or choroid) and pan-uveitis (anterior chamber, vitreous and retina or choroid). Duration of disease is defined as limited if equal to or less than a duration of 3 months, and persistent if

greater than a duration of 3 months. The course is defined as acute if the onset is sudden and duration is limited, recurrent if there are repeated disease episodes with periods equal to or greater than 3 months of disease inactivity, and chronic when the disease is persistent and relapses within 3 months of no therapy. Anterior uveitis is most commonly due to Behcet's disease and viral infections, especially herpes simplex virus (HSV), varicella zoster virus (VZV) and cytomegalovirus (CMV), sarcoidosis, Lyme disease and syphilis. Posterior uveitis causing retinitis and/or choroiditis, can be due to toxoplasmosis, CMV, human immunodeficiency virus (HIV), HSV, VZV, fungal (Candida), parasitic (toxocariasis, cysticercosis) and bacterial infections, sarcoidosis and masquerade forms. These masquerade syndromes may include lymphomas, leukemias, foreign bodies, amyloidosis, juvenile xanthogranulomas, tuberculosis, hepatitis C and Whipple's disease.<sup>60, 61</sup> Pan-uveitis may be seen among others- in Vogt-Koyanagi-Harada disease, a systemic inflammatory condition characterized by a pan-uveitis, often granulomatous, of sudden onset, which may be associated with neurologic, dermatologic and auditory involvement.<sup>62, 63</sup>

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