LETTER TO THE EDITOR

To the Editor

Uveitis and the Diagnosis of Multiple Sclerosis

Keywords: autoimmune disease, immunology, inflammatory diseases, multiple sclerosis, neuro-ophthamology, ophthalmology, optical imaging, vision

Multiple sclerosis (MS) is an inflammatory disease defined by the presence of demyelinating lesions of the central nervous system (CNS) that are disseminated in both time and space. MS is associated with uveitis, an inflammatory condition of the uvea and retina. However, uveitis is not included in the diagnostic criteria for MS, and most neurologists do not consider uveitis to be an MS-related inflammatory event. The immunopathological events in the eyes of MS patients with uveitis share a striking similarity to the inflammatory events in the CNS of MS patients. The purpose of this article is to provide evidence of the similar pathophysiology between MS and MS-associated uveitis in order to prompt further investigation into the inclusion of MS-associated uveitis as part of the clinical definition of MS.

Uveitis is a heterogeneous disease, and in developed countries the etiology is usually inflammatory and autoimmune. Classification of uveitis is based on the predominant anatomical site of inflammation; patients are diagnosed with either anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis. The subtype of uveitis that is most commonly associated with MS is intermediate uveitis (also called vitritis or pars planitis, the latter more specifically defined as vitritis with pars plana exudates).[1] Uveitis can be further classified as granulomatous or nongranulomatous based on clinical features, and uveitis in MS tends to have granulomatous features. The prevalence of intermediate uveitis in MS has been estimated at 2.7% to 16.2%, approximately ten times more common as in the general population.[1,2] In this type of uveitis, inflammatory cells are found predominantly in the vitreous. The source of these inflammatory cells is the adjacent retinal vasculature (more specifically, the retinal venules). As such, intermediate uveitis frequently occurs in association with retinal periphlebitis, which can be seen clinically as retinal vascular sheathing, or on fluorescein angiography as vascular leakage. Patients with uveitis and retinal periphlebitis are more likely to develop MS than patients with uveitis and no signs of retinal periphlebitis.[1,2] Similarly, in patients with optic neuritis, those with retinal venous sheathing are more likely to develop MS.[3] Involvement of the retinal veins in MS-associated uveitis is an important feature to note, because the retina is part of the CNS.

The retina does not normally contain myelin because this would interfere with its important function of phototransduction. Despite the lack of myelin in the retina, the retinal periphlebitis in MS-associated uveitis is analogous to the venular inflammation that occurs in the brains of MS patients. Histology has shown similar cellular accumulations around the veins in the CNS and retina in MS.[4] Thus, it can be argued that similar inflammatory processes are occurring in the brain and retina of patients with MS-associated uveitis, irrespective of the presence of myelin. Retinal periphlebitis in MS could be considered an MS-associated CNS lesion.

Several lines of evidence suggest that the immunopathological processes in MS and MS-associated uveitis are very similar. MS and intermediate uveitis have been shown to share a common immunogenetic predisposition (HLA-DR15).[1] Studies have shown that T lymphocytes from MS patients react similarly to myelin basic protein and the uveitogenic non-myelin protein arrestin.[5] In fact, there is significant amino acid homology between the immunodominant peptide sequences between these two proteins.[5] Animal data also show evidence that non-myelin proteins shared by the retina/uvea and brain may be involved in the pathogenesis of MS. In the rodent model of experimental autoimmune encephalomyelitis, the systemic administration of T cells specific for the astrocyte-derived S100B protein coexpressed in the Muller cells of the retina results in an extensive inflammation of cerebral white and gray matter along with panuveitis and retinitis.[6] The basic science evidence regarding the immunopathology of MS and MS-associated uveitis suggests that common immunological mechanisms are involved, irrespective of the presence of myelin.

The clinical symptoms of intermediate uveitis and retinal periphlebitis can be variable. Patients with moderate or severe inflammation will often complain of decreased vision, and will eventually present to an ophthalmologist. However, patients with mild inflammation may have minimal or no symptoms and might never be referred to an ophthalmologist for assessment. In one study of 50 consecutive MS patients who received detailed ophthalmological examination, asymptomatic retinal periphlebitis was found in 10% of patients.[7] Detection of retinal periphlebitis in MS could potentially serve as a biomarker of disease activity. One study found that the presence of retinal periphlebitis is associated with MS disease activity (assessed by magnetic resonance and the development of a new relapse within 2 years).[8] Fluorescein angiography is a technique that can assist in the assessment of retinal periphlebitis by demonstrating more vascular leakage than can be seen clinically, and newer ultra-widefield techniques allow visualization of larger areas of retina and offer the potential to detect retinal periphlebitis with even greater sensitivity (Figure 1). It is not yet known whether there is any benefit to having detailed ophthalmological examination for uveitis and retinal periphlebitis, including ultra-widefield fluorescein angiography, performed on all patients with MS or suspected MS. Inclusion of such detailed ophthalmic examination in prospective studies of MS will help better understand this issue. In the routine care of MS patients who develop uveitis, detailed ophthalmologic examination can be useful for determining whether a patient has characteristic features of MS-associated uveitis. This can help neurologists determine if a uveitis attack is likely to be related to MS or not.

Overall, there appears to be strong evidence in the literature to demonstrate that uveitis in MS is related to the immunological pathology that occurs in MS. Uveitis may not be an isolated and unrelated comorbid autoimmune disease that occurs in MS patients. It may in fact be a component of the MS disease process. The retina is a non-myelinated component of the CNS, but the processes that occur in the retina in MS-associated uveitis are similar to those that occur in other myelinated parts of the CNS in MS patients. Thus, the fact that the retina lacks myelin should not exclude this structure as a potential site for MS disease involvement. MS-associated uveitis has characteristic features (i.e. granulomatous intermediate uveitis with retinal periphlebitis), which can be determined by an

https://doi.org/10.1017/cjn.2016.250 Published online by Cambridge University Press

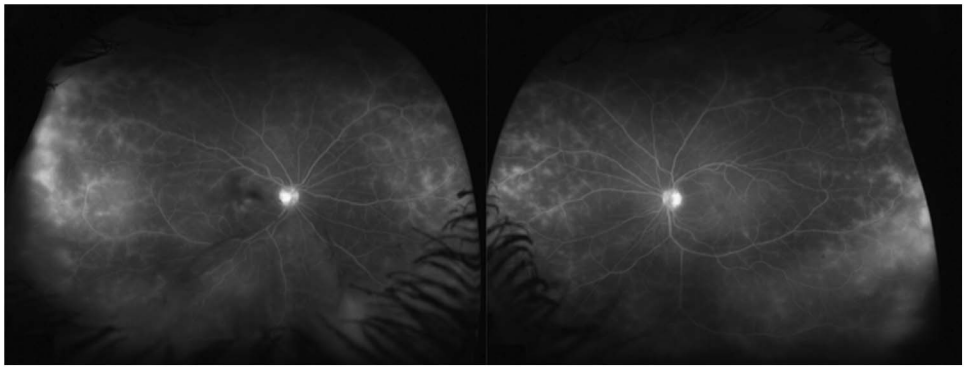

Figure 1: *Ultra-widefield fluorescein angiography in multiple sclerosis (MS)-associated uveitis. On clinical examination, the fundus in this patient with MS-associated uveitis appeared normal, without any signs of retinal periphlebitis. However, ultra-widefield fluorescein angiography shows extensive leakage from retinal veins in both eyes.*

ophthalmologist. The inclusion of MS-associated uveitis in the diagnostic criteria for MS, as well as recognition of uveitis as an MS attack, could potentially lead to earlier diagnosis and treatment of MS and MS attacks. Further prospective studies are warranted in order to investigate the potential diagnostic yield of inclusion of MS-associated uveitis as part of the clinical definition of MS.

Disclosures

The author does not have anything to disclose.

Farzin Forooghian
Department of Ophthalmology
St. Paul's Hospital
Vancouver, British Columbia, Canada

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https://doi.org/10.1017/cjn.2016.250 Published online by Cambridge University Press