

Uveitis and Central Nervous System Demyelination

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A wide range of demographic and clinical features in patients with uveitis increases the likelihood of having associated demyelinating changes on their neuroimaging.

A thirty-year-old female presented with bilateral chronic anterior uveitis. A possible treatment with Tumor Necrosis Factor (TNF) alfa inhibitors was considered. MRI brain scan showed demyelinating changes. The patient was referred to a neurologist who diagnosed her as Multiple Sclerosis (MS) and prescribed interferon.

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Uveitis associated with the central nervous system (CNS) could be classified into demyelinating, infectious, inflammatory/autoimmune and neoplastic. Many of the neurological and ocular inflammatory disorders are poorly understood^{1,2}.

Neurological symptoms present in approximately 8% of uveitis patients. Generally, the ophthalmologist has a low threshold of referring these patients for neurological assessment because of the associated CNS disease, which might be sight-threatening or life-threatening. It is rare for the ophthalmologist to see patients with a primary neurological disorder.

The demyelinating disorders associated with the eye could be divided into two main diseases or conditions: multiple sclerosis (MS) and monosymptomatic optic neuritis (MSON); the latter must be distinguished from MS because it presents with ocular symptoms but no systemic involvement¹. MS is a chronic immune-mediated demyelinating disease of the CNS characterized by relapses and remissions⁴. Optic neuritis is the most common ocular manifestation of MS, occurring in an estimated 30% of patients; however, patients with MS could present with uveitis^{5,6}.

The aim of this presentation is to report a patient who presented with bilateral chronic uveitis and demyelinating disorders.

THE CASE

A thirty-year-old Bahraini female presented with recurrent bilateral anterior uveitis. The patient was considered for Tumor Necrosis Factor (TNF) alfa inhibitor.

The patient gave a history of similar attacks in the last two years and using different types of topical and systemic corticosteroids. She presented with a history of two weeks of bilateral eye pain, redness, photophobia, and a decrease in vision and was on oral prednisolone 1 mg/kg/day. The patient denied any systemic complaints or symptoms; previous serology and blood workups were negative.

On examination, her visual acuity was 6/36 in the right eye and 6/6 in the left. Anterior segment examination in both eyes showed clear cornea with multiple medium-sized keratic precipitates (KPs) and pupil synechia with iris pigments on the lens, see figure 1. She had bilateral anterior chamber reaction of +2 cells. Her lens in the right eye had a significant amount

of posterior subcapsular cataract possibly due to the long term and chronic use of topical steroids, this had obscured a detailed assessment of the vitreous and retina; however, some degree of vascular sheathing and inferior snowballs were seen. Left eye anterior vitreous showed +2 cells with snowball collections and a similar peripheral vascular sheathing to the right eye, her intraocular pressure was normal and the rest of the examination was insignificant, see figure 2.

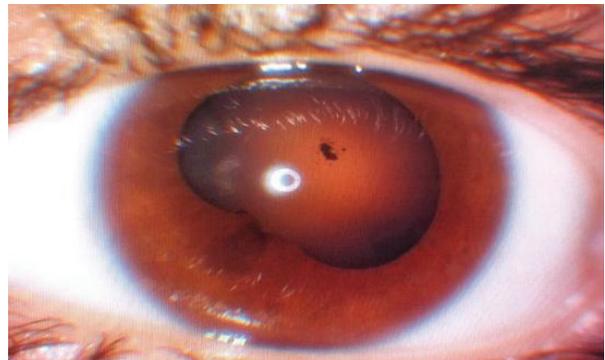


Figure 1: Anterior Segment of the Left Eye Shows Posterior Synechiae and Pigments on the Lens

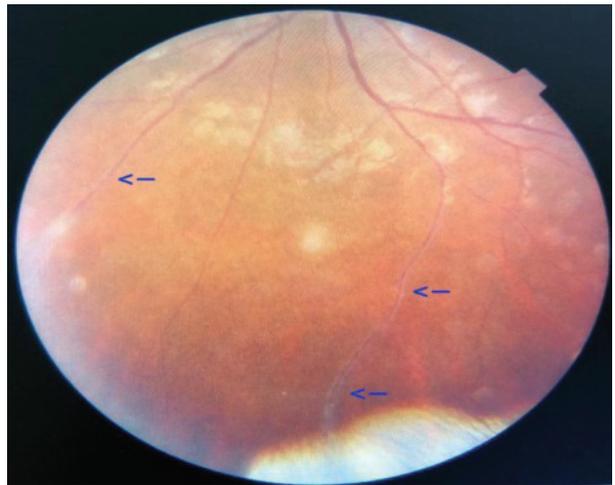


Figure 2: Colored Fundus Photo of the Left Eye Shows Vascular Sheathing (Blue Arrows)

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Fundus fluorescein angiography (FFA) revealed vascular leakage associated with the sheathing seen clinically and confirming the vasculitis in the periphery and mid periphery of the retina, see figure 3. Clinical examination and the FFA changed the initial impression from isolated anterior uveitis to a combination of both anterior and intermediate uveitis associated with retina vasculitis; in a young female, it indicates a possible association of CNS demyelinating disorder.

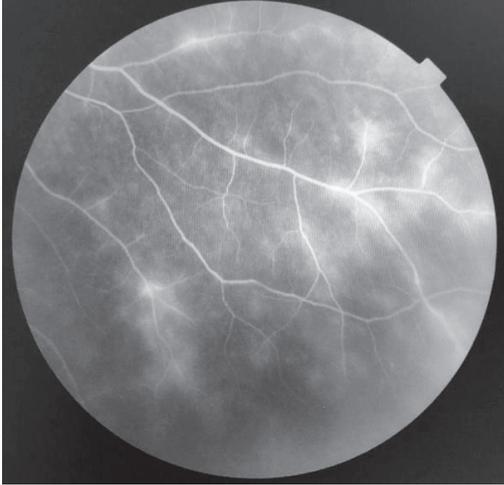


Figure 3: Fundus Fluorescein Angiography of the Left Eye with Leakage and Evidence of Retinal Vasculitis

Brain MRI was requested before the initiation of TNF alpha inhibitors because it is not recommended in demyelinating disease. Brain MRI revealed multiple hyperintense lesions on T2 involving the periventricular and subcortical white matter of supratentorial and infratentorial brain parenchyma, see figure 4. The consideration of TNF alpha inhibitors treatment was dismissed and the patient was referred for neurological consultation. The neurologist diagnosed her with MS and interferon treatment has been started.

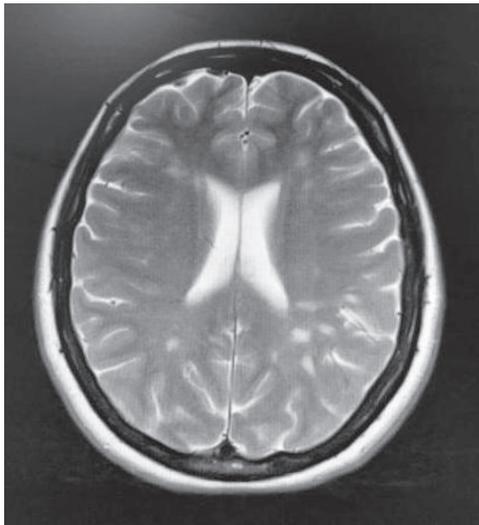


Figure 4: Brain MRI Showing Multiple Hyperintense Lesions on T2 Located in the White Matter

DISCUSSION

Many disorders can affect the eye and the CNS simultaneously or separately. These disorders regardless of their etiology or

pathogenesis present a diagnostic challenge to the physicians and healthcare providers due to the overlap in their clinical manifestations and the difficulty in its interpretations which could be attributed to the anatomical proximity of these two structures and the complex connections between them.

Understanding the embryology and the prenatal development stages of the CNS is very important to reveal the common developmental pathway shared by the eye posterior segment and the CNS. It might clarify the association of uveitis with the CNS disorders and the structural and functional similarities between their protective barriers (the blood-brain barrier and the blood-retinal barrier).

Clinical presentation of uveitis in patients with MS has a prevalence of 0.4 to 28.5%⁶. It could be anterior uveitis, intermediate uveitis, retinal vasculitis, or panuveitis. The intermediate uveitis is the most common type of uveitis in patients with MS and it could occur as an isolated entity or in combination with other types of uveitis⁶⁻⁹. Among patients with intermediate uveitis, approximately 8-20% have MS⁶. The bilateral presentation seems to be the most common; Zein et al found that the disease was bilateral in 15 of 16 patients⁶.

Retinal vasculitis in patients with MS might take different forms, but the prominent one involves the veins. It starts with an active peri-phlebitis phase and later turns into a chronic phase marked by vascular sheathing. Thirty percent of patients with the chronic-progressive type of MS will have some degree of peri-venous sclerosis. Retinal phlebitis in a patient with MS is directly related to the activity of the disease and carries unfavorable prognosis. The association of vasculitis with intermediate uveitis in MS represents a well-recognized anatomopathological sign. The likely explanation of this association between vasculitis and MS is attributed to the common embryological origin of the blood-retinal barrier and the blood-brain barrier.

There is no consensus or guidelines regarding performing a brain MRI in such scenarios. Many of studies found that neuroimaging in patients with intermediate uveitis is warranted due to the high incidence of demyelinating disease; none found a difference in visual outcome in patients with and without demyelinating lesions after brain MRI¹⁰.

Postmortem studies found pathological evidence of MS in patients with no previous neurological symptoms. In 1961, Georgi reported clinically 'silent' MS in 18% of patients from postmortem studies¹¹. In 2009, Moore and Okuda used the term radiologically isolated syndrome (RIS) to describe patients with positive radiological features of MS in their neuroimaging despite the absence of clinical features. MRI scans for unrelated reasons such as trauma or headache were found to have radiological signs suggestive of demyelination. Our patient might be one of these or she might fulfill McDonald's criteria¹².

Performing the brain MRI was justified before TNF alpha inhibitor initiation because of the risk of demyelination¹³. This raises the question of whether it is justifiable to perform an MRI brain to all patients with uveitis before starting them on TNF alpha inhibitors because these agents showed a negative outcome in MS trials^{14,15}. It is a complex subject and many theories have been proposed to explain the relationship between TNF alpha inhibitors and demyelination.

CONCLUSION

The decision of performing MRI should be taken by the neurologist because, from an ophthalmic perspective,

performing MRI will not change the visual outcome of the patient and might burden the patient and the health system. However, the ophthalmologist needs to request MRI if the TNF alfa inhibitors are to be considered as treatment regimen to avoid any future clinical and legal difficulties.

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