Case Report

Oh No! I Can't See Well after Taking a Hot Shower!

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Abstract

This was to report a case of a 33-year-old Malay woman who was previously diagnosed with seronegative neuromyelitis optica spectrum disorder ten years ago based on her clinical presentation, and magnetic resonance imaging (MRI) of the spine showed a long segment of the intramedullary lesion. Her diagnosis was revised to relapsing-remitting multiple sclerosis (RRMS) when she had recurrent optic neuritis with an MRI showing juxtacortical and periventricular lesions. She was started on disease-modifying treatment and was well for six years until she noticed left eye central blurred vision, especially after taking hot showers or exposure to hot weather. Ophthalmological examination revealed left eye visual acuity 6/9 with a relative afferent pupillary defect. Humphrey's visual field also showed left centrocecal scotoma. She was treated with intravenous methylprednisolone with tapering oral prednisolone, which resulted in improvement of the left central scotoma, and her visual acuity reverted to baseline.

Keywords: Multiple sclerosis; optic neuritis; optic neuritis treatment trial; Uhthoff's phenomenon; transverse myelitis

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Introduction

Optic neuritis is an inflammatory condition of the optic nerve sheath. It typically affects young adults aged 18-45 years old (average age of 32 years old) with a greater female gender preference (1). It is highly associated with multiple sclerosis, where 50% of individuals present with features of optic neuritis during their course of illness. Multiple sclerosis is the most common demyelinating disease, causing damage to the protective myelin sheath of the central nervous system. In multiracial Malaysia, the estimated prevalence of multiple sclerosis is about one to two per 100,000 population, with the Malays being the most affected group, followed by the Chinese, Indians and indigenous groups (2).

Recurrent optic neuritis is most seen in patients with multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD) and myelin-oligodendrocyte glycoprotein (MOG) antibody diseases. A study was conducted to identify the patterns of optic neuritis between these three disorders, whereby more than half of the cases in multiple sclerosis had localisation in the same affected eye, which could have contributed to previous tissue damage and disrupted blood-brain barrier (3).

The optic neuritis treatment trial (ONTT) has impacted optic neuritis treatment worldwide. It is proven to shorten the course of disease and reduce ocular morbidity, providing an excellent visual prognosis (4). We reported a case of Uhthoff's phenomenon (UP) in

a woman with relapsing-remitting multiple sclerosis (RRMS) who presented with transverse myelitis.

Case Report

A 33-year-old Malay woman with underlying MS and a strong family history of MS presented with acute left central blurred vision, which progressively worsened for five days duration. This was her third attack with ocular symptoms. The characteristics of this presentation were like the previous ones in which she had left eye blurring of vision, reduced perception of colour, contrast and dull pain upon eye movement, which were worsened by hot showers and exposure to hot weather.

The patient was initially diagnosed with relapsing transverse myelitis ten years ago after two recurrent presentations of back pain, left lower limb numbness and weakness within the same year. The spine's magnetic resonance imaging (MRI) showed a long segment intramedullary lesion from the C3 to C6 levels. The T2 hyperintense lesion is eccentrically located and enhanced with contrast (Fig. 1). She received five days of intravenous methylprednisolone for both presentations. She remained symptomless for four years until she had her first episode of left eye retrobulbar optic neuritis, which was recurrent in the same year. Her MRI of the brain and orbit revealed non-enhancing high signal intensity of the left optic nerve and multiple juxtacortical and periventricular lesions perpendicular to the lateral ventricle, giving rise to Dawson's finger. The periventricular lesions were ovoid; some showed enhancement signifying lesions at different times (Fig. 2). These findings suggested relapsing-remitting multiple sclerosis (RRMS). The diagnosis was also further confirmed by a positive oligoclonal band in her cerebrospinal fluid (CSF). She was then started on self-administered subcutaneous interferon beta 1a thrice a week as a disease-modifying treatment (DMT). She was tolerating well and did not have any further optic neuritis attacks after initiation of the therapy until this current presentation.

On ophthalmological examination, her vision was 6/6 and 6/9 for the right and left eye, respectively, with left relative afferent pupillary defect (RAPD). Her optic nerve function test also showed reduced red saturation and light brightness, with a visual field showing centrocecal scotoma over the left eye, as evidenced by the Humphrey visual field test (Fig. 3). Otherwise, the anterior segment was unremarkable, and her fundus examination revealed a pink optic disc with a well-defined margin. With the impression of

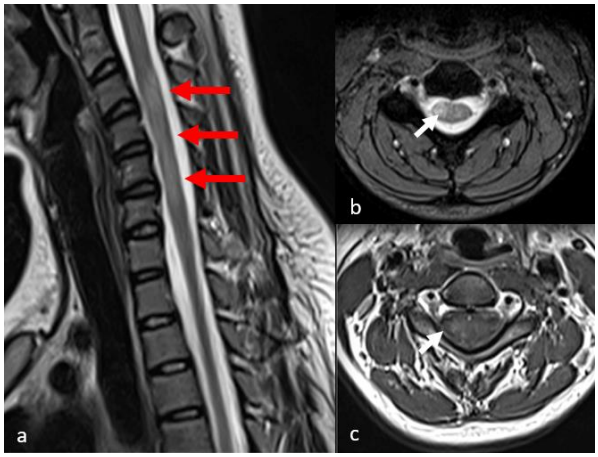

FIGURE 1: MRI of the spine in sagittal T2W (a) axial T2W; (b) and axial T1 post-contrast; (c) A long segment intramedullary lesion spans from the C3-C6 level (red arrows). The lesion was eccentrically located and enhanced post-contrast (white arrows). The spinal cord was relatively normal in size

left eye recurrent retrobulbar optic neuritis, she was also worked up for atypical MS. However, her serum tapering dosage of oral prednisolone for a month, according to the recommendation of ONTT. Her left vision recovered to 6/6 during the subsequent follow-up with no RAPD. Her centrocecal scotoma resolved as well.

Discussion

UP was first described in 1890 by Wilheim Uhthoff, a German ophthalmologist who noticed exercise-induced transient blurring of vision in patients with multiple sclerosis (5). It is defined as the temporary worsening of neurological symptoms due to increased body temperature seen in demyelinating disorders, usually lasting up to 24 hours (6). Other general symptoms include fatigue, muscle stiffness, dizziness, urinary urgency and pain. When Uhthoff investigated this phenomenon, he thought exercise was the primary aetiology of visual loss instead of raised body temperature. His observation, made 133 years ago, had sparked many interests of other scientists to investigate this phenomenon further. Many theories have been formulated to explain this condition. However, the exact mechanism of UP remains unknown.

In the 1980s, hot bath tests were used to elicit the UP before the neuroimaging modality, such as magnetic resonance imaging, existed. In 1995, Saul RF et al. studied how hyperthermia affected the central conduction pathways in normal and demyelinated optic nerves by observing changes in the pattern of

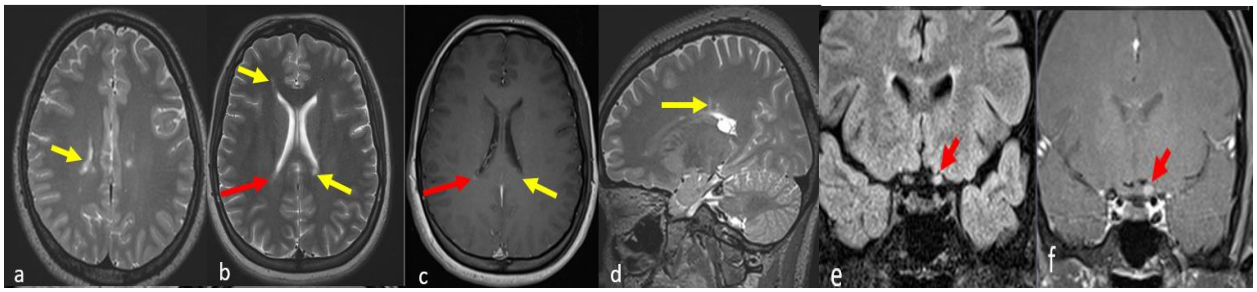

FIGURE 2: MRI of the brain and orbit in axial T2W (a&b) T1W post-contrast; (c) sagittal T2W; (d) and coronal flair; (e) and T1 fat sat post-contrast; (f) multifocal hyperintense periventricular lesions, the majority ovoid in shape (yellow arrows), were seen. Some lesions were perpendicular to the lateral ventricle, giving rise to Dawson's fingers (yellow pointer in d). Enhancement of the lesion can be appreciated (red arrow in c). The left optic nerve was hyperintense and swollen, demonstrating some enhancement post-contrast (red contrast (red arrow in e and f)

visual evoked potentials (7). Loss of amplitude in the nervous conduction pathway of the demyelinated optic nerves group was more significant due to impaired current activity of the denuded nerve fibres but was temporary and reversible. Davis et al. observed a rise of 0.8°C in body temperature, which reduces the speed of adduction of the eyeballs due to the reduced conduction velocity of nerve fibres. Still, they were reversible by cooling (8). Leavitt et al. investigated the correlation between fatigues caused by raised body temperature in patients with RRMS (9). He discovered that greater endogenous body temperature was linked to more exhaustion. In the Japanese traditional culture, taking baths in onsen (natural hot springs) is widely popular and worsening neurological deficits are seen in increased body temperature of patients with MS. A Japanese study conducted by Park et al. discovered treatment with oral 4-aminopyridine, a type of potassium channel inhibitor, was able to restore nerve conduction in demyelinated fibres by action potential prolongation (10). The FDA-approved drug Dalfampridine is an extended-release drug proven to enhance the walking capability and speed in patients with MS (11).

One of the pathophysiology principles behind UP is largely attributed to impaired axonal conduction in demyelinated nerve fibre, where fast saltatory conduction is transformed into slow membrane conduction and reduction in action potential speed (12). Heat prolongs the channel inactivation time, causing a delay in subsequent action potentials. A temperature rises between 0.2°C and 0.5°C can deactivate the sodium channels in axons and halt the action potential's depolarisation phase (13). Safety factor plays an important role in neuromuscular transmission. It is defined as the ratio of the current available to initiate an action potential to the minimal current required. This safety threshold for high-fidelity nerve transmissions is compromised in MS individuals; therefore, even a minor increase in temperature will result in the blockade of the sodium channels in demyelinated axons, causing an impairment in depolarisation activity (14). Both demyelination and hyperthermia contribute to the reduction in the axon's safety factor. Other complex aetiologies involved in these changes include heat

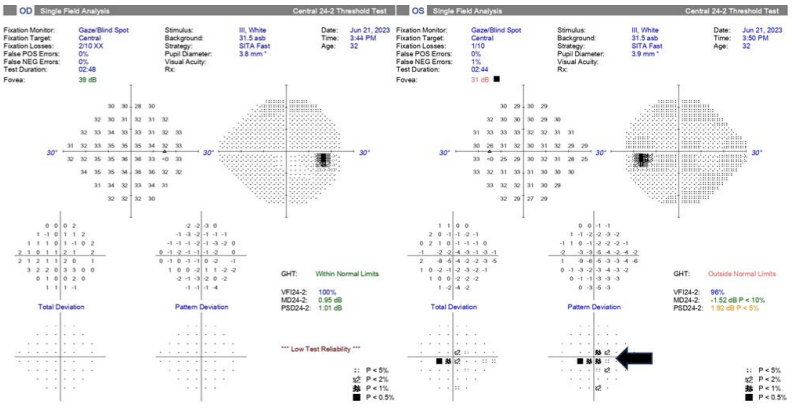

FIGURE 3: Humphrey visual field 24-2 showed left centrocecal scotoma (black arrow) compared to a normal right visual field

shock proteins and unknown humoral substances surrounding the myelinated nerve fibres.

UP triggered by heat exposure is observed in 60-80% of MS patients (15). However, there is a lack of literature regarding UP in our Malaysian population. An article dated 1994 by Tan CT where Malaysian MS patients were found to be heat-sensitive toward increased temperature in 'hot bath tests' but of much lower percentage compared to the Caucasians (16).

In 75% of patients affected with MS, the initial presentation involves an isolated complaint, of which around 50% are motor or sensory and 25% are visual. For our patient, transverse myelitis represented her first onset of MS, which manifested as back pain, lower limb numbness and weakness. Therefore, a thorough systematic review is crucial when it comes to suspicion of multiple sclerosis (17). The signs and symptoms include motor, sensory, autonomic, visual, cognitive and psychological symptoms.

A total of 75% of MS patients experience optic neuritis at least once in their lifetime. However, more than two-thirds of patients affected with optic neuritis have a normal fundoscopic exam in which there is an absence of optic disc swelling or pale disc. This is known as retrobulbar optic neuritis (RBON). Clinical evaluation with optic nerve function tests is essential for diagnosing RBON. Optic nerve assessment includes best corrected visual acuity (BCVA), RAPD, confrontational visual field testing and colour vision testing with particular attention to red desaturation. Reduced colour perception and contrast usually precede vision loss in optic neuritis. These subtle signs could provide significant information in making an early diagnosis of optic neuritis, as visual acuity is usually unaffected during the early phase.

MRI of the brain plays a crucial role in cases of atypical optic neuritis (e.g., significant & progressive visual loss, poor visual acuity, relapse after steroid withdrawal) to further exclude other disease processes. It can yield predictive information on the patient's potential future risk of MS development (18). In cases of isolated optic neuritis attack, a baseline abnormal MRI brain is a strong predictor for MS, as stated in the ONTT trial.

NMOSD and MS are autoimmune inflammatory disorders of the central nervous system (CNS) with similar features. UP is most commonly observed in patients with MS but can also be seen in NMOSD (10). Differentiating between MS and NMOSD is essential for early effective therapy. The discovery of the AQP4 antibody provides a highly sensitive and specific method of diagnosing NMOSD. Dawson's finger-type, periventricular, and inferior temporal lobe lesions are more commonly associated with MS. In contrast, longitudinally extensive transverse myelitis (usually involving more than three vertebral contiguous segments) and peri ependymal brainstem lesions are more to be characteristics of NMOSD. The latter will require a longer course duration of corticosteroid treatment and additional immunosuppressant therapy (e.g., Rituximab, Eculizumab) and may be associated with a poorer visual outcome.

ONTT had several significant advancements in understanding the differences between the outcome of untreated optic neuritis and the effects of low and high-dose corticosteroids. Visual function recovered faster in the intravenous corticosteroids group than in the placebo group. However, the usage of oral prednisone alone is associated with an increased risk of optic neuritis recurrence. Later studies showed no improvement in long-term visual outcomes with steroids but only accelerated recovery (19). Steroids do not affect the long-term risks in the development of MS. Researchers are looking into potential neuroprotective drugs that can lessen or prevent axonal loss and a possible role for optical coherence tomography (OCT) in treatment decisions for optic neuritis.

Disease-modifying drugs (DMD) are reserved for cases which are established with multiple sclerosis. Available choices of DMDs are interferon, monoclonal antibodies like natalizumab, and immunomodulators like glatiramer acetate (GA) and fingolimod. Interferon beta-1a (Rebif) is available in the form of subcutaneous injections administered three times weekly in doses of 22 mcg or 44 mcg. Numerous clinical trials like CHAMPS, PRISMS and BENEFIT have investigated the effectiveness of interferon in different dosages and their efficacy in delaying the onset and relapse rate of MS (20). Side effects associated with interferon beta-1a are flu-like illness, weakness, lethargy, myasthenia, raised liver enzymes and leukopenia. Immunomodulators such as Fingolimod and Glatiramer acetate are used specifically for RRMS and have proven to be highly effective in reducing the relapse rate of RRMS. It does not exclude significant side effects such as bradycardia, macula oedema, melanoma and pulmonary infections (21). Immune reconstitution therapy (IRT) such as Alemtuzumab and Cladribine is now available for a short duration of treatment and has given a longer remission rate with drug freedom for young patients with MS. Non-selective IRT such as Alemtuzumab has a higher risk of developing an autoimmune disorder, hence longer and closer

monitoring is mandatory. Side effects of Alemtuzumab are colds, nausea, fatigue and allergic reactions. For women of childbearing age, it is advised to discontinue DMD treatment before conceiving to minimise the risk of foetal harm (22).

Conclusion

In a tropical country like Malaysia, active cooling measures such as cooling garments, cold showers, ice packs, air-conditioning, and cold beverages should be taken to provide relief to MS patients with UP. However, visual acuity and fundus examination might be normal in subclinical optic neuritis. Hence, performing other optic nerve function tests such as visual field assessment, colour vision, and contrast sensitivity is crucial. In addition, patients' education on subclinical manifestations of optic neuritis attack is important for earlier detection and prevention of sight-threatening conditions or irreversible blindness.

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