

Neuromyelitis optica: The clinical role of the anti-aquaporin 4 autoantibody

Ka-Wai Kam,¹ MBBS, MRCSEd (Ophth), Nelson K. F. Yip,¹ FRCS (Edin), Alexander Y. L. Lau,² MBBS, MRCP, FHKAM (Medicine), Vincent C. T. Mok,² MD, FRCP, FHKAM (Medicine), MRCP, Alvin L. Young,¹ MMedSc (Hons), FRCS(irel)

¹Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong SAR, China.

²Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong SAR, China.

Correspondence and reprint requests:

Dr. Alvin L. Young, Chief of Service, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong SAR, China.

Email: youngla@ha.org.hk

Abstract

Neuromyelitis optica, also known as Devic's disease, involves inflammation of the optic nerve and the spinal cord. It runs a variable clinical course and may result in blindness. Unlike multiple sclerosis, neuromyelitis optica is a separate clinical entity with its own diagnostic criteria that include the presence or absence of anti-aquaporin 4 autoantibody. The effects of the disease are thought to be mediated by autoantibodies that are targeted against the water channel protein, aquaporin 4. In this case report, we highlight the clinical features and the role of this antibody in the diagnosis of patients with neuromyelitis optica.

Key words: Multiple sclerosis; Neuromyelitis optica; Optic nerve; Optic neuritis

Introduction

Optic neuritis is quite frequently encountered in patients with multiple sclerosis (MS) and is the presenting feature in approximately 20% of such patients.¹ Nonetheless, the presence of optic neuritis is not pathognomonic for MS and may form part of other entities such as neuromyelitis optica (NMO). We present a patient whose diagnosis employed the diagnostic value of anti-aquaporin 4 autoantibody.

Case report

A 45-year-old Chinese woman presented to the Accident and Emergency Department of our hospital with an acute

painless reduction in vision of her left eye with superior visual field loss for 1 day in August 2011. The patient had a history of right eye optic neuritis that had been diagnosed at another hospital and was managed conservatively. On examination, her visual acuity was 20/100 and 20/70 for her right and left eye, respectively. Intraocular pressure of both eyes was normal. A positive relative afferent pupillary defect was detected in the right eye. Fundal examination revealed a pale disc on the right side, and a clinically unremarkable left disc. There were no other neurological or ocular deficits. Her clinical diagnosis was left retrobulbar optic neuritis.

Computed tomography of the brain and orbits was unremarkable. Initial blood tests were all normal except for raised antinuclear antibody titer at 1:640 with a speckled and nucleolar pattern on fluorescent examination. Anti-double-stranded DNA was normal at 12 IU/ml. Antinuclear cytoplasmic antibody was negative. Magnetic resonance imaging (MRI) of the brain and orbits revealed non-specific hyperintense T2 foci with perineural enhancement, compatible with left optic neuritis (**Figures 1 and 2**). There was no other radiological evidence suggestive of MS.

She was subsequently treated as per the Optic Neuritis Treatment Trial.² After 2 weeks, the oral steroid was tapered off and at her last visit, her left eye visual acuity had returned to 20/15.

She had a history of suspected viral brainstem encephalitis managed at another hospital in June 2007 when she presented with dizziness, right-sided facial numbness, as well as upper and lower limb numbness with subsequent progression to involve her left upper limb 1 week later. A series of MRI of the brain and spinal cord were performed and revealed an abnormal T2 signal in the left inferior

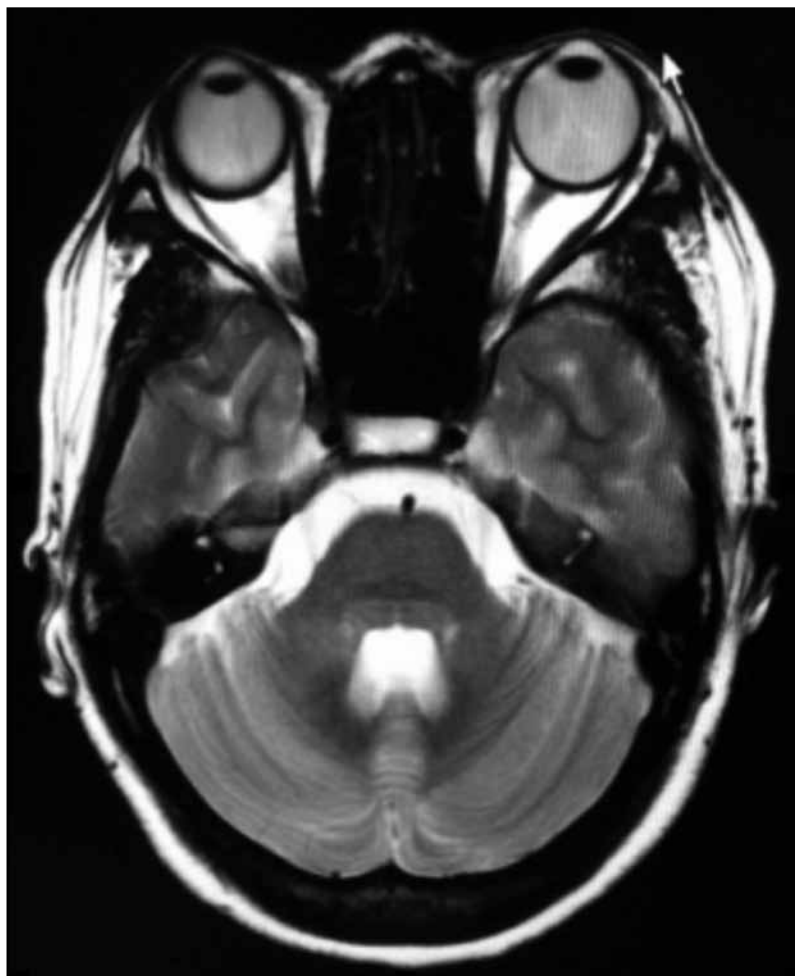


Figure 1. Perineural enhancement of the left optic nerve on T2-weighted magnetic resonance image.

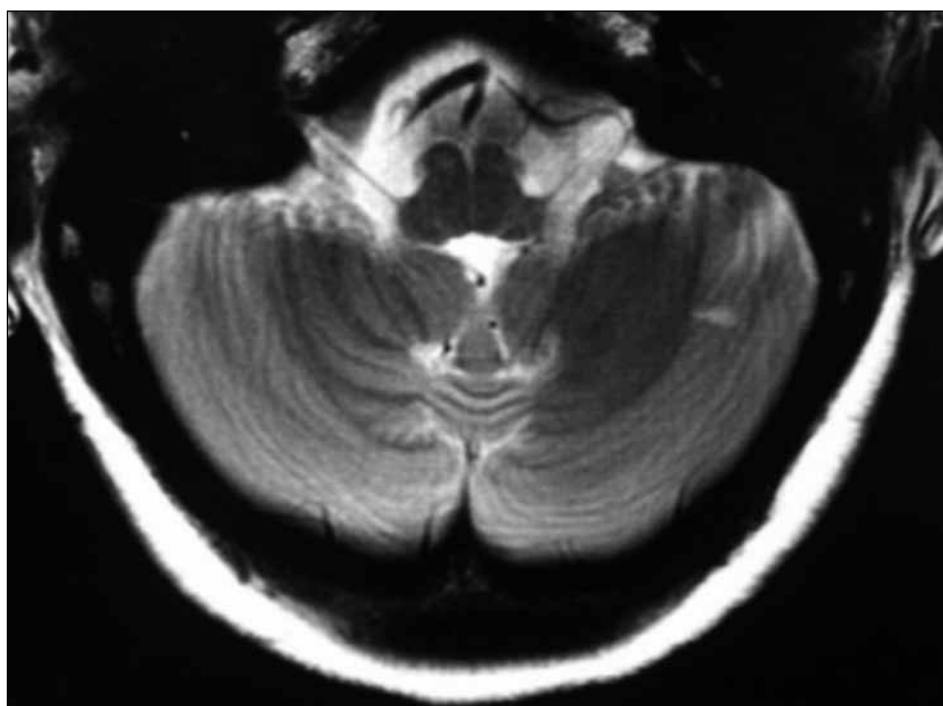


Figure 2. Non-specific hyperintense focus in left cerebellum on T2-weighted magnetic resonance image.

Table. Revised diagnostic criteria for neuromyelitis optica³

Absolute
Optic neuritis
Acute myelitis
Supportive (2 out of 3)
Contiguous spinal cord magnetic resonance image lesion extending over 3 vertebral segments
Brain magnetic resonance image not meeting diagnostic criteria for multiple sclerosis
Aquaporin 4 antibody seropositive status

cerebellar peduncle initially considered as an infarct. Around 2 weeks later there were 2 other T2 hyperintense signals in the left cerebellar hemisphere. The medulla appeared swollen and hyperintense on T2-weighted and fluid-attenuated inversion recovery images, with the hyperintense changes extending to the upper C2 and C3 cervical spinal cord. The radiological findings were compatible with her clinical presentation.

During that admission, cerebrospinal fluid (CSF) analysis revealed normal glucose and total protein levels, white blood cell of $23 \times 10^6/L$ with predominantly lymphocytes (60%). CSF cytology was negative for malignant cells. Enterovirus polymerase chain reaction and oligoclonal band were negative. CSF culture was negative for mycobacteria. Paired sera were sent for viral serology that included measles virus, adenovirus, influenza virus types A and B, *Mycoplasma pneumoniae*, and varicella zoster virus. All were negative, as was rickettsial serology. Weil-Felix agglutination and peripheral blood cultures were also negative. Transcranial Doppler imaging revealed bilateral middle cerebral artery acceleration with mild acceleration of the distal basilar artery.

Later in the same admission she was diagnosed with acute demyelinating encephalomyelitis of presumed viral origin, and given a course of systemic ceftriaxone, doxycycline, and intravenous immunoglobulin treatment with slight improvement in terms of frequency of muscle cramps. Nonetheless, mild residual dystonia and occasional right-sided paraesthesia remained despite a period of rehabilitation.

In May 2011, she developed an episode of right optic neuritis that was managed at another hospital. MRI of the brain and orbits revealed no evidence of MS or any definite signs of optic neuritis. She declined any steroid treatment and her residual visual acuity for her right eye remained at 20/100.

In view of the presence of recurrent optic neuritis and a history of myelitis, subsequent anti-aquaporin 4 autoantibody titer testing was performed and was positive. According to the diagnostic criteria by Wingerchuk et al in 2006,³ the presence of 2 absolute criteria of recurrent optic neuritis and transverse myelitis, alongside 2 out of 3

supportive criteria, namely absence of radiological features of MS, longitudinally extensive transverse myelitis of more than 3 segments, and a positive serum titer for anti-aquaporin 4 antibody, constitutes a positive diagnosis of NMO. At the end of the day, since the myelitis in our patient did not extend beyond 3 segments, the positive status of anti-aquaporin 4 antibody was the determining factor in the diagnosis of our patient.

Discussion

NMO was once considered a variant or subtype of MS, though recent studies have revealed growing evidence that it is a separate clinical entity.^{4,5} Prevalence studies of the condition are scarce and unknown in Hong Kong even though NMO is considered more common among non-Caucasians, and particularly among Asians.⁶ The prevalence of NMO has been described as 3.1 per 100,000 in a Japanese population⁷ compared with an estimated 0.3 to 4.4 per 100,000 in a western population.⁸ Women are more commonly affected and the age of onset is often during the fourth decade of life. In contrast to NMO, MS has a higher global prevalence that ranges from 90 to 193 per 100,000 population in Europe and America, to 1 to 41 per 100,000 population among Asian populations in India, China, Japan, and Hong Kong.⁹

NMO is an inflammatory condition that affects primarily the optic nerves and the spinal cord. The disease is considered to be antibody-mediated, as the pathology of spinal cord lesions of these patients reveals vasculocentric deposits of complements, immunoglobulins, and macrophages indicating a mechanism mediated by antibodies.¹⁰

In 2004, Lennon et al¹¹ identified aquaporin 4, a commonly found water channel protein in the central nervous system, as the target antigen of this antibody; 2 years later, the same group from the Mayo Clinic revised the diagnostic criteria of NMO to include 2 absolute criteria of recurrent optic neuritis, an episode of acute myelitis, alongside 3 supportive criteria that included absence of radiological features of MS, contiguous spinal cord MRI lesion extending over 3 vertebral segments, and the presence of anti-aquaporin 4 autoantibody (**Table**).³ The diagnosis of definite NMO can

only be made when the 2 absolute criteria and any 2 of the 3 supportive criteria are present.

Conclusion

In conclusion, NMO is a distinct clinical entity that is mediated by an autoantibody targeting aquaporin 4 protein and has to be distinguished from MS. The condition often presents as a chronic relapsing disease with isolated or

recurrent optic neuritis and / or transverse myelitis, clinical patterns that resemble those of MS. Hence, the detection of anti-aquaporin 4 autoantibodies was very important in our patient whose clinical manifestations did not fulfill Wingerchuk et al's criteria for diagnosis of NMO.³

Declaration

The authors declared no conflict of interest in this study.

References

1. Beck RW, Trobe JD, Moke PS, et al. High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the optic neuritis treatment trial. *Arch Ophthalmol*. 2003;121:944-9.
2. Volpe NJ. The optic neuritis treatment trial: a definitive answer and profound impact with unexpected results. *Arch Ophthalmol*. 2008;126:996-9.
3. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology*. 2006;66:1485-9.
4. Jarius S, Wildemann B. AQP4 antibodies in neuromyelitis optica: diagnostic and pathogenetic relevance. *Nat Rev Neurol*. 2010;6:383-92.
5. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology*. 1999;53:1107-14.
6. Thornton IL, Rizzo JF, Cestari DM. Neuromyelitis optica: a review. *Semin Ophthalmol*. 2011;26:337-41.
7. Kuroiwa Y, Igata A, Itahara K, Koshijima S, Tsubaki T. Nationwide survey of multiple sclerosis in Japan. Clinical analysis of 1,084 cases. *Neurology*. 1975;25:845-51.
8. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurol*. 2007;6:805-15.
9. Pugliatti M, Sotgiu S, Rosati G. The worldwide prevalence of multiple sclerosis. *Clin Neurol Neurosurg*. 2002;104:182-91.
10. Papadopoulos MC, Verkman AS. Aquaporin 4 and neuromyelitis optica. *Lancet Neurol*. 2012;11:535-44.
11. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet*. 2004;364:2106-12.