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VIEWS AND REVIEW

The role of anti-aquaporin-4 antibody in Asian patients with multiple sclerosis: Confusions and controversies

HT Chong, *AG Kermode, CT Tan

*Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia; *Australian Neuromuscular Research Institute, Sir Charles Gairdner Hospital, Western Australia, Australia*

Abstract

Neuromyelitis optica (NMO) was first described as a severe monophasic syndrome of acute bilateral optic neuritis and transverse myelitis. Whether it is a form of multiple sclerosis (MS) or a separate disease entity has been continually debated since the beginning of last century. The redefinition of NMO as a relapsing disease, the wider use of magnetic resonance imaging showing longer spinal cord lesion, and the recently discovered anti-aquaporin-4 (AQP4) water channel antibody, or NMO-IgG, has rekindled this controversy. The many recent publications including the abstracts published in this issue of *Neurology Asia* have shown that anti-AQP4 antibody is of variable sensitivity in different populations. It appears to be associated mainly with longitudinal extensive spinal cord lesions and frequent relapses. The site of pathology of NMO also do not co-localize with the widespread expression of AQP4 in the body, throwing doubts on the suggestion that the anti-AQP4 antibody plays primary role in the pathogenesis of NMO. In the day-to-day clinical practice in Asia, anti-AQP4 antibody remains a research investigatory test. As for optic-spinal MS, which is closely similar to NMO based on recently revised criteria, interferon should remain the treatment of first choice.

HISTORICAL DEVELOPMENT OF NEUROMYELITIS OPTICA

Neuromyelitis optica (NMO) was first described by Allbutt in 1870. Sporadic case reports and small pathological studies were published in the years that followed, but it was in 1894 when Devic and his student Gault described 17 patients who had a severe monophasic syndrome of acute transverse myelitis with bilateral optic neuritis that the name NMO was given.[1,2] Many cases of the early reports had pathological changes in the brainstem and cerebrum, which in retrospect probably included a variety of conditions such as acute disseminated encephalomyelitis and multiple sclerosis (MS), and perhaps even infections, such as syphilis.[2]

The debate of whether NMO is a form of MS first started nearly 80 years ago. As early as 1927, pathological studies showed that the inflammation in NMO was more severe and was not only associated with demyelinating plaques, but also with cavitation, necrosis and acute axonal pathology in both the grey and white matter.[2-4] However, pathological reports since 1882 had also reported similar findings in MS, and these had been confirmed in many subsequent studies.[2] As early as 1942 patients who initially diagnosed as NMO were reported to develop other neurological signs consistent with MS later.[2]

MULTIPLE SCLEROSIS IN ASIA

Studies in Asia in the 1970s, especially in Japan, showed that the clinical features in a proportion of Asian patients with MS were dissimilar from that seen in Western countries. These patients had recurrent optic neuritis and transverse myelitis and, apart from minor brainstem signs and symptoms, had little evidence of disease elsewhere and the term optic-spinal form of MS was used to describe them. In Asia, the term Devic disease or NMO was used to refer to a monophasic disease with bilateral optic neuritis and severe transverse myelitis, as defined by Shibasaki, McDonald and Kuroiwa in 1981.[5] The difference between optic-spinal MS and NMO then was that the latter is a monophasic disease and the former, a recurrent one.[2] Other significant

Address correspondence to: Dr HT Chong, Neurology Laboratory, University Malaya Medical Centre, 59100 Kuala Lumpur, Malaysia. E-mail: hengtchong@yahoo.co.uk

differences between the Asian MS and that of the West included higher female preponderance, more severe optic nerve and spinal cord disease, a rarity of family history, lower frequency of oligoclonal bands and cerebellar involvement among the Asian patients.[6]

RECENT CONTROVERSY ON NEUROMYELITIS OPTICA

With the widespread use of magnetic resonance imaging in the diagnosis of MS in the 1990's, it was found that patients with NMO had fewer or no brain lesions, but rather they had spinal cord lesions longer than two vertebral segments in length.[7,8] Based on this, and other reports, the debate that whether NMO is a separate disease from MS was rekindled.[4,9-11] It was also claimed without much evidence that NMO responds to different forms of treatment from MS; that is, patients with NMO responded better to immunosuppressive such as azathioprin rather than immunomodulatory treatment such as β-interferon therapy.[11] Having been redefined to include recurrent disease, NMO is now very similar to optic-spinal MS among Asians, and thus this controversy has important implication in Asian neurology practice.[10]

MRI study in the Asia Pacific region showed that the paucity of brain lesions was common among Asian MS patients, including those whose clinical features were indistinguishable from their Western counterparts. Long spinal cord lesions, defined as lesions longer than two vertebral segments, were also not uncommon in Asian patients; in fact 29% of Asian MS patients had lesions longer than two vertebral segments.[13] A review of the literature showed that even among Western MS, at least 10% had minimal or no brain lesions[14] and long spinal cord lesions were seen in 10-36% of patients.[15-18] This suggests that there is not only a great heterogeneity in the clinical features of MS, but also a large degree of overlap between different forms of MS, including that of optic-spinal form, modified by racial differences.

ANTI-AQUAPORIN-4 ANTIBODY, IS IT SPECIFIC TO NEUROMYELITIS OPTICA?

It is in this backdrop of continual debate of nearly 80 years that in 2004, an autoantibody against the aquaporin-4 (AQP4) water channel was reported to be associated with NMO. The antibody was initially termed NMO-IgG, indicating its close link to NMO[19], which is now also known as anti-AQP4 antibody. The antibody assay was found to be 73% sensitive and 91% specific for NMO, and 58% sensitive and 100% specific for optic-spinal MS in the initial report.[19] This study spawned a new diagnostic criteria.[20] The latest reports from Asia and Australia in this issue of *Neurology Asia* however, painted a very different picture. Firstly, the sensitivity of the test was more variable than reported; being only 5.6% to 27.1% in some reports; only half of the 58% sensitivity rate for optic-spinal MS as initially reported. On the other hand, 1.9% - 5.6% of patients with conventional, Western, form of MS and 25% of patients with idiopathic transverse myelitis were found to be positive.[22,23] More interestingly, the presence of the antibody was associated with brain MRI fulfilling Barkhof criteria[23], which is against the recently proposed revised diagnostic criteria for NMO that requires that the brain MRI does not meet the diagnostic criteria for MS.[20] The presence of anti-AQP4 antibody is also associated with the presence of long cord lesion, irrespective of whether it is conventional or optic-spinal MS, and, on multivariate analyses, the number of relapses.[23-25] For the latter, the results of the largest screening study done in Japan so far, by Niigita University, showed that the average relapse rate in the patients with positive antibody was 3.64 per-annum.[24,25] This suggests that the antibody may be associated with the severity of the disease, particularly in the spinal cord.

One of the reasons for these differences could be the different methodology used in detecting the antibody. However, in a comparative study using sera predetermined by the Mayo clinic, the test in question was shown to be at least 83% sensitive and 100% specific.[23,24] The differences seen then, were not due to technical reason.

DOES ANTI-AQUAPORIN-4 ANTIBODY PLAYED A PRIMARY ROLE IN PATHOGENESIS OF NEUROMYELITIS OPTICA?

Another controversy was the assertion that the anti-AQP4 antibody was involved in the pathogenesis of NMO[21], and perhaps also optic-spinal MS. The main arguments being that in a minority of NMO patients, MRI showed that some of the lesions co-localized with AQP4 distribution in the central nervous system and pathological studies of these lesions showed a loss of AQP4.[26] However, only 6.7% of NMO patients had lesions that co-localized with the AQP4 water channel[27] whereas at least 10% of them had MRI findings that met

Barkhof's criteria and at least 60% had lesions in the white matter, away from sites with abundant AQP4.[28] The loss of AQP4 water channels in the lesions may reflect the severity of the inflammation and the associated cell death since the level of other astrocytic markers such as glial fibrillary acidic protein (GFAP) was also found to be decreased in the lesions.[29] It was also noted early on that the ubiquitous expression of AQP4 water channel in the brain, cerebellum, as well as in the stomach and kidneys, is paradoxical in the face of the typical, restricted involvement of the optic nerve and the spinal cord in NMO.[19]

Takahashi[21] mentioned the high sensitivity and specificity of anti-AQP4 antibody to support the antibody's involvement in the pathogenesis of NMO. As mentioned above, the sensitivity and specificity of anti-AQP4 antibody to NMO or optic-spinal MS were more variable than initially reported. Takahashi[21] also mentioned the correlation between the titres of anti-AQP4 antibody and acute relapses as a proof of the pathogenecity of the antibody, though this could merely reflect the severity of the inflammatory process. Indeed, the development of the antibody could be a secondary phenomenon in response to the intensity of the inflammatory process. It has been shown by the same authors that unless the titre was above 1:512, the antibody was not found in the central nervous system[21], though titre above 1:40 was routinely accepted as positive. Therefore in a proportion of anti-AQP4 antibody positive patients (whose titre was between 1:40 to 1:512 dilutions) the antibody was not detectable in the central nervous system, and this is in contradiction to the belief that the antibody was the primary cause of inflammation in the restricted sites of the optic nerve and spinal cord in the central nervous system. The titre has also been found to be related to the presence of other autoantibodies, such as anti-SSA/SSB or antinuclear antibodies, suggesting rather a general, non-specific humoral response.[24]

ROLE OF ANTI-AQUAPORIN-4 ANTIBODY IN NEUROLOGY PRACTICE IN ASIA

As the debate continues, the average practicing neurologist in Asia is faced with the day-to-day decision with regards to the diagnosis and treatment of these patients.

What is the role of anti-aquaporin-4 antibody in day-to-day Asian clinical practice?

With regards to diagnosis, the pertinent question is the role of anti-AQP4 antibody test in day-to-day clinical practice in Asia, since currently there is only one available service provider for the test which performs it on a commercially basis. Although there are a few other institutions in the region, mainly in Japan, which could perform the test, it is mainly done as part of research or investigatory studies. Current available studies suggest that firstly, there is insufficient evidence to confidently redefined NMO (or the optic-spinal form of MS) as an entity distinct from MS. Secondly, anti-AQP4 antibody test has also not been consistently shown to be specific in the diagnosis of the redefined NMO (or optic-spinal MS). Thirdly, the claim that anti-AQP4 antibody plays a primary role in the pathogenesis of NMO is still in doubt. Therefore, we believe that in the day-to-day clinical practice in Asia, anti-AQP4 antibody remains a research or investigatory test. Further prospective longitudinal studies with careful clinical and radiological assessments should be done in different and unselected populations to clarify its association and significance.

Should the treatment of optic-spinal multiple sclerosis be modified in the presence of anti-aquaporin-4 antibody?

The next question is whether the treating physicians should modify the treatment if the patients were found to have the anti-AQP4 antibody, or in a patients with a high risk of harboring the antibody, such as one with longitudinal extensive spinal cord lesions.[23-25] Currently there is limited evidence to indicate the effectiveness of immunosuppressive treatment aimed at reducing serum autoantibody levels.[30] Conversely, the only double blind study based on immunomodulation therapy among Asians has shown the effectiveness of β-interferon in relapsing and remitting MS, including optic-spinal form of the disease[31], although some preliminary data suggested that patients with positive anti-AQP4 antibody and severe spinal cord disease may do less well.[12] The authors thus believe that β-interferon should continue to be the treatment of first choice among patients with optic-spinal MS, including those with longitudinal extensive spinal cord disease.

Use of term neuromyelitis optica in Asia

The final comment is with regard to terminology. As the average length of the spinal MRI lesion is longer than 3 vertebral segments among Asians

with MS[13], many patients who has been classified optic-spinal MS may fulfill the revised criteria of NMO.[20] There are strong advocates for using immunosuppressive treatment for treatment of NMO[32] despite the absence of objective evidence at this stage, yet the most robust evidence favors immunomodulatory therapy with β-interferon in optic-spinal MS among Asians.[31] Words used may sometimes have unintended consequences. A change of diagnostic label from optic-spinal MS to NMO may mean a denial of payment for the costly interferon treatment by the insurance agencies or government health care providers, which in turn means a denial of the use of the potentially effective immunomodulatory treatment in these patients. The authors believe that there should be special care when the term NMO as defined by the revised criteria[20] is being used in patient care and medical communication in Asia, particularly during didactic teaching to general medical audience and students, who may not appreciate the complexities of the issues. There should be utmost caution before optic-spinal MS is used interchangeably with NMO.

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