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MULTIPLE SCLEROSIS JOURNAL | MSJ

Research Paper

Multiple Sclerosis Journal
17(9) 1067–1073
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DOI: 10.1177/1352458511403958
msj.sagepub.com
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Frequency and syndrome specificity of antibodies to aquaporin-4 in neurological patients with rheumatic disorders

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Abstract

Background: A new autoantibody (termed NMO-IgG, or AQP4-Ab) has recently been described in patients with neuromyelitis optica (NMO) and its *formes frustes*, longitudinally extensive transverse myelitis (LETM) and recurrent optic neuritis (rON). However, AQP4-Ab has been found also in patients with co-existing rheumatic diseases such as systemic lupus erythematosus (SLE) or Sjögren's syndrome (SS), conditions which are characterized by broad, polyspecific B cell activation.

Objectives: In this study, we aimed at evaluating the syndrome specificity and frequency of AQP4-Ab in patients with rheumatic diseases and neurological symptoms.

Methods: For this purpose, serum samples from 109 neurological patients with established connective tissue disorders (CTD) ($n = 54$), possible CTD ($n = 42$), or vasculitis ($n = 13$) were analysed for the presence of AQP4-Ab by a cell-based assay employing recombinant human AQP4.

Results: AQP4-Ab was detectable in 31/40 (78%) patients with CTD and NMO spectrum disorders (median titre, 1:1000) but in none of the samples obtained from patients with CTD or vasculitis and neurological disorders other than NMO, LETM, or rON ($n = 69$).

Conclusion: The high syndrome specificity of the antibody for neuromyelitis optica spectrum disorders (NMOSDs) in patients with CTD supports the concept of AQP4-Ab being involved in the pathogenesis of these neurological conditions, and argues against AQP4-Ab simply being part of the polyclonal B cell activation generally associated with rheumatic diseases. Moreover, the finding that AQP4-Ab is present in patients with CTD and co-existing NMOSD with approximately the same frequency as in patients without CTD strengthens the case of CTD and AQP4-Ab positive NMOSD representing two co-existing yet distinct entities in the majority of patients.

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Keywords
antibody to aquaporin-4, connective tissue disorders, diagnosis, longitudinally extensive transverse myelitis, neuromyelitis optica (Devic's disease), neuropsychiatric lupus, NMO-IgG, rheumatic diseases, scleroderma, Sjögren's syndrome, systemic lupus erythematosus, vasculitis

Date received: 7th July 2010; revised: 19th December 2010; 20th February 2011; accepted: 22nd February 2011

Introduction

Neuromyelitis optica (NMO) is a very rare inflammatory disorder of the central nervous system (CNS) of putative autoimmune aetiology, which mainly affects the optic nerves and spinal cord.[1] Recent studies demonstrated that NMO and its *formes frustes*, longitudinally extensive transverse myelitis (LETM)[2] and recurrent optic neuritis (rON),[3,4] are associated with the presence of a newly detected serum reactivity to structures adjacent to the CNS microvasculature and pia mater in 60–80% of cases (called NMO-IgG).[5,6] This antibody was later shown to target aquaporin-4 (AQP4), the most abundant water channel in the CNS.[7,8]

Interestingly, AQP4-Ab was found also in a subset of NMO and LETM patients with co-existing connective tissue disorders (CTDs) such as systemic lupus erythematosus (SLE) or Sjögren's syndrome (SS).[9] However, CTDs are usually associated with a broad repertoire of autoantibodies, many of which are of no proven pathogenic impact. AQP4-Ab could be part of that polyclonal B-cell response in patients with CTD rather than being pathogenetically related to the neurological syndrome.

Strong evidence for a role of AQP4-Ab in the pathogenesis of NMO and LETM/rON in patients with CTD would come from the demonstration that the antibody is present only in patients with CTD and NMO or LETM/rON but not in patients with CTD and neurological disorders other than NMO and LETM/rON.

Here we report on the AQP4-Ab serostatus of 109 patients with established or suspected rheumatic diseases and co-existing neurological disorders.

Patients and methods

Inclusion criterion was the presence of SLE, SS, systemic scleroderma, polymyositis/dermatomyositis, Sharp syndrome, or vasculitis at the time of neurological presentation, or of autoantibodies usually associated with those disorders. Exclusion criterion was the presence of co-existing conditions that could sufficiently explain the neurological syndrome, such as infections, or stroke due to well established causes other than CTD. Group I consisted of 54 patients with definite CTD and neurological involvement (see Table 1 for details). CTD in this group comprised SLE ($n = 41$), primary SS (6), SLE with secondary SS (2), systemic sclerosis (1), systemic sclerosis with SS (1), scleroderma en coup-de-sabre (1), CREST syndrome (1), and Sharp syndrome with biopsy proven polymyositis (1). Group II consisted of 42 patients with various neurological syndromes (Table 1), who were positive for auto-antibodies usually associated with CTD but who did not fulfil the formal criteria for any CTD based on the data available for analysis. Anti-nuclear antibodies were present in 40/42, SS-A and/or SS-B in 13, cardiolipin and anti-ß2-glycoprotein antibodies in 16, double stranded DNA antibodies in nine, ribonucleoprotein antibodies in nine, lupus anticoagulans in three, Scl-70 antibodies in two, histon antibodies in three, and centromer antibodies in five; three patients were, in addition, positive for rheumatoid factor and one for single strand DNA antibodies and circulating immune complexes. Further features of CTD such as Raynaud's phenomenon, sicca symptoms, polyserositis, nephritis, or arthralgia were present in 16 patients; in addition, Coombs' positive anaemia was reported in one, and other haematological disturbances in seven. Group III consisted of 13 patients with vasculitis. Seven patients had primary arteritis of the CNS (PACNS), four giant cell arteritis, one leukocytoclastic vasculitis, and one post-infectious systemic vasculitis involving the CNS.

All SLE patients fulfilled the American College of Rheumatology (ACR) criteria.[10,11] SS was diagnosed according to Vitali et al.[12] and scleroderma according to Masi et al.[13] The diagnosis of PACNS was established according to Moore and Richardson[14] in 5/7 cases and according to Calabrese and Mallek[15] in two cases. NMO was diagnosed according to Wingerchuk's 2006 criteria.[1] LETM was defined as myelitis extending over three or more vertebral segments. NMOSD followed a relapsing course in 36 patients and was monophasic in four.

Samples were tested for AQP4-Ab in an anonymized fashion at the Department of Neurology, University of Heidelberg by means an indirect immunofluorescence assay employing human full length AQP4 expressed

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Table 1. Rheumatic diagnoses and neurological syndromes, epidemiological data and serum AQP4-Ab results from neurological patients with established or possible connective tissue disorders or vasculitis

Diagnostic groups and neurological syndromes	*N*	Sex (m:f)	Age (median, range)	AQP4-Ab*N* (%)
Definite CTD	54	1:20	46 (16–75)	16 (30)
NMO spectrum disorders	21			16 (76)
NMO	15			10 (67)
LETM	5			5 (100)
rON	1			1 (100)
Syndromes other than NMO/LETM/rON	33			0 (0)
Possible CTD	42	1:3.6	45 (21–79)	15 (36)
NMO spectrum disorders	19			15 (79)
NMO	12			10 (83)
LETM	6			4 (67)
rON	1			1 (100)
Syndromes other than NMO/LETM/rON	23			0 (0)
Vasculitis	13	1:12	52 (35–88)	0 (0)

NMO: neuromyelitis optica, LETM: longitudinally extensive transverse myelitis, rON: recurrent optic neuritis.

in HEK293 cells.[16] Briefly, formalin-fixed AQP4-transfected HEK293 cells, which were provided immobilized on microscopy slides, were incubated with serum or CSF diluted 1:10 in 1% bovine serum albumin and, after washing in PBS, with a goat anti-human IgG antibody conjugated to fluorescein isothiocyanate (FITC). After final washing in PBS and mounting in glycerol containing an anti-fading agent, cells were analysed for bound AQP4-IgG on a Nikon 90i fluorescence microscope (Nikon Imaging Center, University of Heidelberg, Germany). This assay was previously shown to have a sensitivity of 78% and a specificity of 100% ($n = 151$).[16] All patients were of Caucasian origin. Sex ratios in the various diagnostic groups as well as median age at blood sampling are given in Table 1.

Results

AQP4-Ab was detectable in 20/27 (74%) samples from patients with definite or possible rheumatic diseases and NMO, in 11/13 (85%) samples from patients with rheumatic diseases and LETM or rON, but in none out of 69 samples obtained from patients with rheumatic diseases and neurological disorders other than NMO, LETM, or rON ($p < 0.00001$; Fisher exact test). Neurological disorders or symptoms in the latter group included longitudinally non-extensive transverse myelitis, demyelinating disease of the brain, brain infarction, (micro)bleedings of the brain, aseptic meningitis, seizures, trigeminal neuralgia, polyneuropathy, mononeuritis, ataxia, depression and other psychiatric syndromes, neuropsychological disorders, myositis, and headache.

The frequency of AQP4-Ab was 84.6% in patients with SLE and NMO or LETM/rON and 62.5% in patients with other CTD and NMO or LETM. AQP4-Ab serum titres in patients with NMOSD and CTD (median, 1:1000; range, 1:50–1:10.000; $n = 19$; definite CTD in 16, possible CTD in three) did not differ significantly from those in a group of unselected control patients with NMOSD but no CTD (median, 1:1000; range, 1:50–1:12.500; $n = 20$). AQP4-Ab was positive in 78% (28/36) of the relapsing cases, and in 75% (3/4) of the monophasic cases. The median maximum longitudinal extension of spinal cord lesions did not differ between AQP4-Ab positive and AQP4-Ab negative NMOSD patients (5 [range, 3–19] and 5.5 [3 to 'entire spinal cord'], respectively), nor did the median total number of relapses (4.5 and 6, respectively).

Cranial lesions as detected by MRI were present in 17/40 (43%) NMOSD patients, with no significant difference between AQP4-Ab positive (12/31) and negative cases (5/9). Brain stem MRI lesions were noted in 6/31 AQP4-Ab positive NMOSD patients (19%) and in 3/9 AQP4-Ab negative NMOSD patients (33%), and were situated in the medulla oblongata in six patients (AQP4-Ab positive in five) and in the pons in two (AQP4-Ab positive in one). Brain stem involvement was also suspected in some additional AQP4-Ab positive patients based on clinical presentation (vomiting and tonic fits in one, and diplopia in two), though

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MRI was negative. In two patients with brain stem lesions, both of which were AQP4-Ab positive, additional lesions in the diencephalon (thalamus in two, hypothalamus in one), mesencephalon (cerebral peduncle), basal ganglia (capsula interna), and cerebellar peduncles were observed; in addition, cerebellar lesions were evident in one of them. Supratentorial white matter MRI lesions were noted in 32% (10/31) of the AQP4-Ab positive and 22% (2/9) of the AQP4-Ab negative NMOSD patients. Periventricular, juxtacortical, or callosal lesions were reported in six of the patients (AQP4-Ab positive in five). Extra-opticospinal neurological manifestations, which are normally absent in patients with NMO,[20] were documented in six AQP4-Ab positive patients and one AQP4-Ab negative patient. These manifestations included psychosis in two (though steroid associated in one of them), cognitive deficits in one, seizures in one, transient ischemic attacks in two, polyneuropathy in two, and polymyositis in one. Three NMOSD patients (AQP4-Ab positive in two) had co-existing acetylcholine receptor antibody positive myasthenia gravis, one of which in addition suffered from coeliac disease.

Thryoid stimulating hormone receptor antibody positive autoimmune thyroiditis with hyperthyroidism (Grave's disease) was present in four patients (AQP4-Ab positive in three) and Hashimoto thyroiditis with hypothyroidism in two (both AQP4-Ab positive). In two additional patients, thyroglobulin or thyroid peroxidase antibodies respectively, but no evidence for thyroid dysfunction, were found, and in two further patients hypothyrodism was noted at least once but anti-thyroid antibodies had not been determined (all AQP4-Ab positive).

One AQP4-Ab positive patient with NMOSD in group I and three AQP4-Ab positive patients with NMOSD in group II were positive for perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) (myeloperoxidase-specific pANCA in two, pANCA of unknown specificity in two); in contrast, 26 other patients with NMOSD (AQP4-Ab positive in 20) were negative for ANCAs. A strong female preponderance was evident both in the NMOSD (sex ratio, m:f = 1:12.3) and in the non-NMOSD (m:f = 1:4.6) group ($p = 0.23$), with no significant difference between AQP4-Ab positive (female in 97%) and AQP4-Ab negative NMOSD patients (female in 78%). See Table 1 for further results.

Discussion

We found that AQP4-Ab seropositivity in patients with CTDs such as SLE or SS and co-existing neurological disorders is restricted to those with NMO, LETM, or rON. The high syndrome specificity of AQP4-Ab in patients with neuropsychiatric CTD argues strongly against the antibody being simply part of the CTD-associated spectrum of non-tissue specific autoantibodies but suggests that it is linked to the pathogenesis of NMO, LETM, or rON in those patients. In previous studies, we and others had already demonstrated a lack of AQP4-Ab seropositivity in patients with CTD but no neurological disease ($n = 45$).[8,9,17] We also found that both the rate of AQP4-Ab seropositivity and the median AQP4-Ab serum titres do not differ significantly between patients with NMOSD and co-existing CTD and patients with NMO but no CTD.

Our results corroborate findings from two smaller studies. Pittock et al. reported a lack of AQP4-Ab in eight patients with CTD and neurological syndromes other than NMOSD from an American cohort and in six patients from a French cohort.[9] In this study, a non-AQP4-specific immunohistochemical assay employing adult mouse cerebellum tissue sections as substrate was used to detect AQP4-Ab. In a second, independent study, Wandinger et al. very recently reported a lack of AQP4-Ab in a mixed British–German cohort with neurological syndromes but not NMOSD.[17] This study, which employed the same recombinant assay as used here, included 41 patients with CTD and neurological syndromes other than NMOSD, but only three patients with CTD and NMO (compared with 27 in the present study).

The finding of AQP4-Ab in a subset of patients with CTD and NMO, LETM, or rON identifies these cases as part of the newly described spectrum of autoimmune AQP4-channelopathies.[7,18,19] Future trials on neurological involvement in CTD have to take into account that AQP4-Ab positive patients may represent a distinct subgroup with differential pathogenesis and treatment response. Similarly, this finding has implications for everyday clinical practice. AQP4-Ab positive LETM or rON usually takes a relapsing course and confers a high risk of conversion to NMO, which, if untreated, often results in irreversible blindness and immobility within a short time.[2,4,20] Although no controlled treatment trials exist in NMO due to the rarity of the disorder, long term immunosuppression, e.g. with azathioprine or rituximab, is thought to be crucial in AQP4-Ab positive patients, and plasma exchange seems to be beneficial for the treatment of acute relapses.[21–25]

The reason why AQP4-Ab positive NMO/LETM is frequently associated with CTD is unclear. It has been speculated that the co-existence of the two disorders in the same patient might reflect a general autoimmune predisposition. The concept of coexisting independent, antibody-mediated autoimmune disorders in the same patient is further supported by the association of AQP4-Ab positive NMOSD with autoimmune conditions such

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as Grave's disease, myasthenia gravis, or coeliac disease, as observed in this study as well as in previous ones.[26–30]

In addition, CTD-induced tissue damage might well promote AQP4-Ab-induced pathology. There is increasing evidence for a direct impact of AQP4-Ab in the immunopathogenesis of NMO/LETM.[18,19,31–33] Briefly, the antibody is thought to confer tissue damage by complement activation and induction of a cellular immune response.[31,32,34–38] However, several findings indicate that AQP4-Ab may not be sufficient to cause CNS disease on its own. First, AQP4-Ab remains detectable in patients with NMO during remission, partly at high titres,[39] and is even detectable many years prior to disease onset in some patients.[40,41] Secondly, in animal models of NMO, passive transfer of the antibody into rodents had no effect unless disruption of the blood–brain barrier or brain inflammation was induced.[31,32,42]

Importantly, aquaporin-4, the target antigen of AQP4-Ab, is an integral constituent of the blood–brain barrier. The protein is concentrated in the astrocytic endfeet sealing the brain parenchyma against the brain vasculature. Vascular damage induced by CTD-associated vasculitis might thus both render AQP4 accessible to AQP4-Ab and, in addition, create the inflammatory environment required for induction of the AQP4-Ab-mediated inflammatory cascade. Interestingly, four AQP4-Ab positive patients with NMO/LETM were positive for pANCA, antibodies frequently associated with vasculitis, in the present study.

It should be underlined, however, that CTD, though a possible promoter, is not a prerequisite of disease activity in NMO. Pittock et al.[9] systematically investigated the frequency of ANA as a sensitive and early marker of CTD associated autoimmunity, and could demonstrate a lack of ANA positivity in around 40% of AQP4-Ab positive NMOSD patients. Accordingly, the onset of NMOSD preceded the occurrence of clinical or serological signs of CTD related autoimmunity in at least five of our patients, who only later in the disease course developed SLE ($n = 3$; AQP4-Ab positive in two) or SS ($n = 2$; AQP4-Ab positive in one). Moreover, the priority of CTD in time noted in many patients does not necessarily imply a causal relationship. Instead, at least in patients with SLE, it might simply reflect the differential peaks of onset of the two conditions (30 years of age in SLE,[43] 40 in relapsing NMO[20]).

Importantly, 9/39 patients with NMOSD were negative for AQP4-Ab in our study, suggesting that NMOSD might be aetiologically heterogeneous. In a previous study, we found AQP4-Ab in 95/96 serum samples that were obtained during remission and under treatment with immunosuppressants such as azathioprine, rituximab, cyclophosphamide, mitoxantrone, or dexamethasone, rendering it unlikely that AQP4-Ab seronegativity in those nine patients was caused by treatment effects.[39] Alternatively, tissue damage might be caused by CTD-mediated mechanisms (e.g. vasculitis) in those patients. Moreover, so far unknown autoantibodies might play a role, as indicated by the fact that plasma exchange was found to be beneficial also in some AQP4-Ab negative patients in a recent study.[44]

Seven patients had extra-opticospinal disorders such as PNP or seizures, which are not usually associated with AQP4-autoimmunity. The presence of extra-opticospinal signs and symptoms should prompt physicians to check for co-existing CTD.

Given the number of centres involved in this study, we cannot fully exclude that some sort of sampling bias might have influenced the data on AQP4-Ab frequency in CTD and NMO spectrum disorders. However, this study did not primarily aim at assessing the frequency of AQP4-Ab but the syndrome specificity of this new antibody in patients with CTD. Moreover, the frequency found in this study (77%) is in good accordance with data from two smaller previous studies.[9,17]

It is of note that antibodies to AQP4 in patients with CTD and NMO/LETM were investigated by means of a recombinant assay instead of immunohistochemistry (IHC) in this study. Recombinant assays have repeatedly been demonstrated to be more sensitive and slightly more specific than IHC.[16,35,45–48] The test used in this study had a 12.5% higher sensitivity when compared with standard IHC on adult mouse cerebellum sections and a specificity of 100% ($n = 151$).[16]

In conclusion, our data demonstrates that AQP4-Ab is highly specific for NMO/LETM in patients with CTD. This finding strengthens the case of AQP4-Ab being involved in the pathogenesis of NMO/LETM in patients with CTD. AQP4-Ab testing should be performed in all patients with CTD presenting with signs and symptoms suggestive of NMO, LETM, or ON.

Acknowledgements

The cells used in this study were kindly provided by Euroimmun, Luebeck, Germany. We are grateful to Professor Maria K Storch (Medical University of Graz) and Dr Franziska Di Pauli (Medical University of Innsbruck) for their support and cooperation, and to Mrs Anna Eschlbeck, Mrs Brigitte Fritz, and the Nikon Imaging Center at the University of Heidelberg for excellent technical assistance.

Funding

This work was supported by a Research Fellowship from the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) to SJ, research grants from Bayer Schering Pharma and from Merck Serono to BW, a grant from the German Research Foundation (DFG; Cluster of Excellence 257) to FP, and a research grant of the Austrian multiple sclerosis research society to MR.

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Conflict of interest statement

KPW is an employee of Euroimmun, Luebeck, Germany. Euroimmun provided the cells used in this study, but had no influence on study design, analysis or interpretation of data, or the decision to publish this manuscript. The other authors declare no competing financial interest.

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