NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE

Article No: 59

Arch Neuropsychiatry 2026;63:375–379
https://doi.org/10.29399/npa.29290

Aquaporin-1 Antibodies in Autoimmune Inflammatory Demyelinating Disorders with Predominant Optic Nerve & Spinal Cord Involvement

Erdem TÜZÜN[1], Eleni KARACHALIOU[2,3], Maria PECHLIVANIDOU[2], Dimitrios TZANETAKOS[3]
Cem İsmail KÜÇÜKALİ[1], Vuslat YILMAZ[1], Zerrin KARAASLAN[1], Elif ŞANLI[1], Recai TÜRKOĞLU[4]
Murat KÜRTÜNCÜ[5], Tuncay GÜNDÜZ[5], Aliki PAPAKONSTANTINOU[2], Christos STERGIOU[2]
Sotirios GIANNOPOULOS[3], Georgios TSIVGOULIS[3], John TZARTOS[2,3]

[1]Department of Neuroscience, Aziz Sancar Institute of Experimental Medicine, Istanbul University, Istanbul, Türkiye
[2]Tzartos NeuroDiagnostics, Athens, Greece
[3]Second Department of Neurology, School of Medicine, "Attikon" University Hospital, National and Kapodistrian University of Athens, Athens, Greece
[4]Department of Neurology, Istanbul Haydarpasa Numune Training and Research Hospital, Istanbul, Türkiye
[5]Department of Neurology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Türkiye

ABSTRACT

Introduction: Antibodies to the extracellular domain of the astrocytic aquaporin-1 (AQP-1) have been reported in patients with neuromyelitis optica spectrum disorder (NMOSD) and a few multiple sclerosis (MS) patients with predominant spinal cord involvement. Our aim was to identify the prevalence and clinical correlates of antibodies against AQP1 (AQP1-Abs) in a broader spectrum of autoimmune inflammatory demyelinating central nervous system (CNS) disorders.

Methods: Sera from patients with NMOSD (n=30), recurrent inflammatory optic neuropathy (RION) (n=15), relapsing remitting MS (RRMS) (n=69), of which 10 had optic neuritis and/or short myelitis, and healthy controls (n=36) were screened for the presence of AQP1-Abs by ELISA and for antibodies against aquaporin-4 (AQP4-Abs) and myelin oligodendrocyte glycoprotein (MOG)-Abs by cell-based assays.

Results: AQP1-Abs were found in 11% of patients with optic neuritis and/or myelitis [6.7% of NMOSD, 13.3% of RION and 20% of RRMS with optic neuritis and/or short myelitis]. None of the RRMS patients without optic neuritis and/or short myelitis and none of the healthy controls had AQP1-Abs. The two AQP1-Abs-positive RRMS patients, who fulfilled Barkhof criteria by virtue of MRI lesion distribution, had experienced ≥4 short myelitis and/or optic neuritis attacks.

Conclusion: AQP1-Abs are occasionally detected in autoimmune inflammatory demyelinating CNS disorders highlighting optic nerve and spinal cord involvement.

Keywords: Aquaporin-1, neuromyelitis, multiple sclerosis, antibody, autoimmunity

Cite this article as: Tüzün E, Karachaliou E, Pechlivanidou M, Tzanetakos D, Küçükali Cİ, Yılmaz V et al. Aquaporin-1 Antibodies in Autoimmune Inflammatory Demyelinating Disorders with Predominant Optic Nerve & Spinal Cord Involvement. Arch Neuropsychiatry 2026;63:375–379. doi: 10.29399/npa.29290

INTRODUCTION

Aquaporins (AQPs) are transmembrane proteins playing an essential role as water channels in different cell types including astrocytes (1). Aquoporin-4 (AQP4) has been well established as the target autoantigen in neuromyelitis spectrum disorder (NMOSD), an autoimmune astrocytopathy leading to demyelination, and antibodies (Abs) to AQP4 are involved in the pathogenesis of NMOSD (2). More recently, Abs targeting the extracellular domain of aquaporin-1 (AQP1), another astrocytic water channel, have been detected in patients with NMOSD and longitudinally extensive transverse myelitis (LETM) (3). It is well known that astrocytes of cerebral white matter, optic nerve, and spinal cord express AQP1 (4) and AQP1 expression is increased in the brain of multiple sclerosis (MS) patients, possibly to maintain water homeostasis (4,5). Abs against AQP1 have also been found in a few MS patients with predominant spinal cord involvement and patients with isolated short transverse myelitis (6).

Highlights

- **AQP1-Abs are detected in opticospinal demyelinating disorders.**
- **AQP1-Abs are identified for the first time in recurrent optic neuropathy.**
- **AQP1-Abs occur in MS with optic nerve and spinal cord attacks.**

The presence of Abs to AQP1 in non-NMOSD patients has led to the speculation that AQP1 autoimmunity might also be involved in other autoimmune disorders predominantly targeting spinal cord and optic

Correspondence Address: Erdem Tüzün, Istanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Neuroscience, İstanbul, Türkiye • **E-mail:** drerdem@yahoo.com
Received: 28.11.2025, **Accepted:** 29.12.2025, **Publication Date:** 26.03.2026

nerves. However, the exact significance of AQP1-Abs in autoimmune inflammatory demyelinating brain disorders other than the NMOSD phenotype is not well-characterized. To identify the prevalence of AQP1-Abs and its exact clinical correlates in a broader spectrum of autoimmune inflammatory demyelinating central nervous system (CNS) disorders, we screened sera of patients with NMOSD, MS and recurrent inflammatory optic neuropathy (RION) for the presence of AQP1-Abs and other NMOSD-related Abs.

METHODS

Subjects

This study includes 30 NMOSD patients fulfilling the relevant diagnostic NMOSD criteria (7), 15 RION patients, 69 consecutively enrolled relapsing remitting MS (RRMS) patients satisfying the revised McDonald's 2017 criteria for clinically definite MS (8) and 36 healthy individuals. None of the included RRMS patients had developed LETM during the disease course. Only RION patients with three or more isolated optic neuritis episodes and a follow-up period of at least 5 years were included. All RION patients had normal cranial and spinal magnetic resonance imaging, chest X-ray, blood biochemistry, total blood count, vitamin B12, and folate levels and were negative for thyroid Abs and anti-nuclear Abs. Sera collected from all participants were aliquoted and stored at -80°C freezer until use. All patients that were included in the study were in remission and none of the patients were under immunosuppressive treatment during serum sampling.

Demographic features, duration of disease, expanded disability status scale (EDSS) scores and oligoclonal band (OCB) types of all patients were noted (Table 1-3). Blood samples were collected from all patients during recruitment and all patients were followed-up between 3.2–8.8 years after blood sampling. Magnetic Resonance Imaging (MRI) images were obtained with the same 1.5 Tesla scanner during the sampling and whenever attacks occurred during the follow-up. Progression to secondary progressive MS (SPMS) was recorded for MS patients during the follow-up period.

Attack types were defined based on clinical features only. Optic neuritis attack was defined as acute onset visual loss in one or both eyes and myelitis attack was defined as acute onset loss of motor and/or sensory functions in both lower or all four limbs (with or without bladder, bowel or sexual dysfunction). Supratentorial hemisphere involvement was considered for patients exhibiting motor and/or sensory impairment in unilateral arm and leg. Symptoms congruent with involvement of the

Table 1. Clinical features of AQP1-Ab^{pos} patients with autoimmune inflammatory demyelinating disorders

Age/ Sex	Disorder	MOG-Abs/ AQP4-Abs	First symptom	Disease duration (years)	EDSS	OCB type	ON	SC	ST	BS	T2-weighted MRI lesions during follow-up
68/F	NMOSD	– /+	ON	4	3.5	1	+	+	-	-	LETM
47/M	NMOSD	– / –	ON	3	5.5	1	+	+	-	-	LETM
29/F	RION	– / –	ON	1	1.0	1	+	-	-	-	Normal
27/F	RION	+/ –	ON	7	1.5	1	+	-	-	-	PVL, SCL*
43/F	RRMS	– / –	SC	22	3.0	1	+	+	-	+	PVL, JCL, BSL, SCL**
36/F	RRMS	– / –	SC	1	1.0	2	-	+	-	-	PVL, JCL, SCL**

ON: clinical features congruent with optic nerve involvement; SC: clinical features congruent with spinal cord involvement; ST: clinical features congruent with supratentorial central nervous system involvement; BS: clinical features congruent with brainstem involvement.
*MRI findings do not fulfill Barkhof criteria [10], non-specific white matter lesions not typical for multiple sclerosis (white matter lesions with a diameter of ≥5 mm, an ovoid shape and perpendicular to the corpus callosum and ventricles were described as typical multiple sclerosis lesions).
**MRI findings fulfill Barkhof criteria [10].

Table 2. Comparison of clinical and demographic features of AQP1-Abs^{pos} and negative patients with autoimmune inflammatory demyelinating disorders

	AQP1-Abs positive (n=2)	AQP1-Abs negative (n=67)
Age	39 (36–43)	29 (17–56)
Sex (women/men)	2/0	37/30
Duration of MS (years)	11.5 (1.0–22.0)	3.1 (1.0–27.0)
EDSS	2.0 (1.0–3.0)	1.8 (0.0–5.5)
Follow-up after blood sampling (years)	4.8 (4.5–5.0)	5.8 (3.2–8.8)
Conversion to SPMS during follow-up	0	8
OCB +	1	50
ON	1	40
SC	2	38
ST	0	59
BS/cerebellar	1	33

Numerical variables are denoted as median (minimum-maximum).
ON: patients with at least one attack congruent with optic nerve involvement during clinical course; SC: patients with at least one attack congruent with spinal cord involvement during clinical course; ST: patients with at least one attack congruent with supratentorial central nervous system involvement during clinical course; BS/cerebellar: patients with at least one attack congruent with brainstem and/or cerebellar involvement during clinical course.

Table 3. Comparison of clinical and demographic features of AQP1-Abs^{pos} and negative relapsing remitting multiple sclerosis (RRMS) patients

	AQP1-Abs positive (n=6)	AQP1-Abs negative (n=108)	p value
Age	39 (27–68)	35 (17–66)	0.235
Sex (women/men)	5/1	67/41	0.411
Disorder	2 NMOSD 2 RRMS 2 RION	28 NMOSD 67 RRMS 13 RION	0.241
AQP4-Abs^{pos}	1	18	>0.999
MOG-Abs^{pos}	1	0	0.053
Duration of disease (years)	3.5 (0.7–22.2)	4.2 (0.0–32.3)	0.430
EDSS	2.3 (1.0–5.5)	2.0 (0.0–7.5)	0.385
EDSS ≥6.0	0	15	0.327
Follow-up after blood sampling (years)	5.0 (4.5–5.0)	5.4 (3.2–8.8)	0.106
OCB +	1	55	0.207

Numerical variables are denoted as median (minimum-maximum).

brainstem nuclei and cerebellar system (with or without accompanying motor or sensory symptoms) were considered as brainstem and cerebellar attacks, respectively. Patients presenting with predominant spinal cord and optic nerve involvement (MS-SCON, n=10) satisfied the revised McDonald's 2017 criteria for clinically definite MS (8), presented with at least one optic neuritis and one myelitis attack, displayed at least four attacks during the disease course, did not experience any LETM attacks and did not satisfy the NMOSD criteria (7).

Cell Culture and CBAs

All sera were screened using the "live"CBA with HEK293 cells expressing the myelin oligodendrocyte glycoprotein (MOG) protein for the detection of anti-MOG-IgG1 Abs as previously described (9). For the detection of anti-AQP4 Abs, fixed CBA was performed using Euroimmune kits (FA 1128–1010–50) as described by the manufacturer.

Enzyme-Linked Immunosorbent Assay (ELISA)

Abs against AQP1 were detected by ELISA with AQP1 and AQP1 synthetic peptides to ensure that Abs bind to the extracellular domain of the protein (3). In brief, detergent solubilized affinity-purified intact human AQP1, expressed in yeast Pichia pastoris (6) or the mixture of 3 peptides corresponding to the 3 extracellular loops of AQP1, or the mixture of 3 peptides corresponding to the 3 intracellular AQP1 domains (6) were plated in wells of 96-well plates as previously (6). Only sera with Abs to the intact AQP1 and to the mixture of peptides corresponding to the extracellular domain of AQP1 were considered positive.

Statistical Analysis

Statistical comparisons were performed by Mann-Whitney U test for numerical data or chi-square test for categorical data and *p*-values of $p<0.05$ were considered statistically significant.

RESULTS

Antibody Results and Clinical Association

Eighteen NMOSD patients had Abs to AQP4, and one RION patient had Abs to MOG. AQP1-Abs were found in 6 patients with autoimmune inflammatory demyelinating disorders of the brain but in none of the healthy controls. The diagnosis was NMOSD for 2, RION for 2 and RRMS for 2 AQP1-Abs^{pos} patients. Thus, AQP1-Abs were detected in 6.7% of NMOSD, 13.3% of RION and 2.9% of RRMS patients. One RION patient was positive for both AQP1 and MOG-Abs and one NMOSD patient was positive for both AQP4 and AQP1-Abs (Table 1). The diagnosis of AQP1-Abs^{pos} patients did not change during the follow-up period (between 4.5–5 years). AQP1-Abs^{pos} RRMS patients fulfilled the Barkhof criteria in terms of distribution of lesions (10) and one RRMS patient showed cerebrospinal fluid OCB. AQP1-Abs were found in 2 of 10 (20%) patients with MS-SCON and none of the remaining 59 MS patients. Notably, although the 2 AQP1-Abs^{pos} RRMS patients exhibited symptoms congruent with optic nerve, brainstem and/or spinal cord involvement, none of these patients developed symptoms clearly suggestive of supratentorial brain involvement (Table 1 and 3).

Comparison of AQP1-Abs Subgroups

The comparison between AQP1-Abs-positive and AQP1-Abs-negative patients showed equivalent age, sex, disorder distribution, disease duration, EDSS and OCB positivity rates. Although it is observed that while none of the positive patients had an EDSS score greater than 5.5, in total 15 AQP1-Ab negative patients had an EDSS score of ≥6.0; this difference did not attain statistical significance (Table 2). Considered as a whole, these findings suggest that the observed differences in EDSS distribution between the two subgroups may be influenced by the limited sample size and should be interpreted with caution.

Due to low number of AQP1-Abs^{pos} RRMS patients, antibody positive and negative RRMS patients were not statistically compared. Nevertheless, AQP1-Abs^{pos} RRMS patients showed comparable age, sex, disorder distribution, disease duration, EDSS and OCB positivity rates. None of the AQP1-Abs^{pos} RRMS patients had an EDSS score of ≥6.0 and they had not converted to SPMS during the follow-up period (Table 3).

DISCUSSION

Our results indicate that AQP1-Abs can be found in patients with a broad spectrum of autoimmune inflammatory demyelinating CNS disorders exhibiting optic nerve and spinal cord involvement. Additionally, we identified AQP1-Abs in patients with RION for the first time. Although MOG antibody has been previously identified in patients with RION with a prevalence ranging between 9–25% (11,12), to our knowledge, this is the first study to show that RION patients with MOG-Abs may also display AQP-1 Abs. While AQP1-Abs are usually found in AQP4-Ab^{neg} NMOSD patients, double-positive AQP1/AQP4-Abs patients may also

rarely be found (13). In our cohort, we have identified one additional double-positive NMOSD patient.

As we reported earlier (6,13), AQP1-Abs are also found in a small fraction of MS patients predominantly presenting with optic nerve, short spinal cord and brainstem lesions. In addition, the present study suggests that AQP1-Abs^{pos} MS patients do not necessarily exhibit LETM and may display cerebrospinal fluid oligoclonal bands while fulfilling the clinical and neuroimaging criteria of clinically definite MS. Notably, we have also recognized that none of the AQP1-Abs^{pos} MS patients included in this cohort had clinical features congruent with supratentorial CNS involvement in their medical history or records. Interestingly, these patients, classified as MS-SCON in our previous studies (14,15), exhibited a higher AQP1-Ab prevalence (2 out of 10 patients – 20%) than other disease types, though given the small sample size, this observation should be regarded as preliminary. Demonstration of Abs to an astrocytic antigen, AQP1, in these patients is in line with our previous reports showing increased prevalence of anti-astrocytic Abs in MS-SCON and RION patients (15,16).

An intriguing question is the pathogenic significance of AQP1-Abs and the mechanisms by which these Abs develop. A putative explanation might be the enhanced expression of AQP1 by the astrocytes of the optic nerve and spinal cord of patients with demyelinating CNS disorders (4,5). The enhanced expression of astrocytic AQP1 might trigger an immune response to AQP1 in genetically susceptible individuals. Alternatively, it is also possible that astrocytes of the optic nerve and spinal cord are more vulnerable to antibody-mediated astrocyte damage.

The broad range of AQP1-Ab –related disorders may imply that AQP1-Abs are produced merely as a reaction to neuroinflammation, characterized by enhanced astrocyte activation and do not have a pathogenic significance. However, the interaction of AQP1-Abs with the extracellular domain of this water channel indicates that these Abs may play a pathogenic role. Also, the demonstration of an AQP1-Abs^{pos} NMOSD patient with reduced cerebral astrocytic AQP1 expression (while AQP4 expression was preserved) and antibody deposition in AQP-1 expressing astrocytes of the white matter suggests the potential involvement of these Abs in disease pathophysiology (17). Intriguingly, as reported in our previous cohort (13), AQP1-Abs^{pos} patients showed trends towards exhibiting lower disability scores compared to seronegative patients; although this trend is based on limited data, it may reflect, possibly due to the relatively low pathogenic activity of the AQP1-Abs.

From a methodological perspective, a limitation of the present study should be acknowledged.

Specifically, the absence of a complementary live cell-based assay for AQP1 warrants cautious interpretation of AQP1 antibody positivity. Future studies combining ELISA with cell-based or functional assays will be essential to further clarify the true prevalence, specificity, and pathogenic relevance of AQP1-Abs in autoimmune inflammatory demyelinating CNS disorders (18).

In conclusion, in this study, we report a possible association between AQP1-Abs and optic nerve/spinal cord involvement in autoimmune inflammatory demyelinating CNS disorders; a finding that highlights the necessity for larger, prospective studies to confirm this observation. Lastly, whether AQP1-Abs carry a pathogenic and prognostic significance needs to be further substantiated through the identification of a higher increased number of AQP1-Ab positive patients, neuropathological studies and the performance of functional antibody assays.

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and approved by the Local Institutional Review Board of the Attikon University Hospital (protocol code B NEUR. EBD 280/17.5.21; date of approval: 27 July 2021) and followed local institutional review board guidelines.

Informed Consent: Written informed consent was obtained from all subjects involved in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- ET, SG, GT, JT; Design- ET, MK, SG, GT, JT, AP, SC; Supervision- MK, TG, ET, SG, GT, JT; Resource- JT; Materials- RT, TG, VY, SG, GT; Data Collection and/or Processing- EK, MP, EŞ, RT, MK, TG, VY, SG, GT, JT; Analysis and/or Interpretation- MK, TG, VY, VK, EK, AP, SC; Literature Search- ET, MP, SG, GT, EŞ, ZK, VY; Writing- ET, EK, MP, DT, CİK, VY, ZK, EŞ, RT, MK, TG, SG, GT, JT; Critical Reviews- ET, MK, SG, GT, JT.

Conflict of Interest: JT is coinventor in a patent that relates to the detection of antibodies to aquaporin 1. All other authors report no conflicts of interest.

Financial Disclosure: This work was supported by the European Union's Horizon Europe research and innovation program under grant agreement no. 101119457 to ET, VY and JST.

REFERENCES

1. Papadopoulos MC, Verkman AS. Aquaporin water channels in the nervous system. Nat Rev Neurosci. 2013;14:265–277. [Crossref]
2. Zekeridou A, Lennon VA. Aquaporin-4 autoimmunity. Neurol Neuroimmunol Neuroinflamm. 2015;2:e110. [Crossref]
3. Pechlivanidou M, Xenou K, Tzanetakos D, Koutsos E, Stergiou C, Andreadou E, et al. Potential role of antibodies against aquaporin-1 in patients with central nervous system demyelination. Int J Mol Sci. 2023:24;12982. https://doi.org/10.3390/ijms241612982 [Crossref]
4. Trillo-Contreras JL, Ramírez-Lorca R, Villadiego J, Echevarría M. Cellular distribution of brain aquaporins and their contribution to cerebrospinal fluid homeostasis and hydrocephalus. Biomolecules. 2022;12:530. [Crossref]
5. Satoh J, Tabunoki H, Yamamura T, Arima K, Konno H. Human astrocytes express aquaporin-1 and aquaporin-4 in vitro and in vivo. Neuropathology. 2007;27:245–256. [Crossref]
6. Tzartos JS, Stergiou C, Kilidireas K, Zisimopoulou P, Thomaidis T, Tzartos SJ. Anti-aquaporin-1 autoantibodies in patients with neuromyelitis optica spectrum disorders. PLoS One. 2013;8:e74773. [Crossref]
7. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International Panel for NMO diagnosis. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85:177–189. [Crossref]
8. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17:162–173. [Crossref]
9. Tzartos JS, Karagiorgou K, Tzanetakos D, Breza M, Evangelopoulos ME, Pelidou SH, et al. Deciphering anti-MOG IgG antibodies: clinical and radiological spectrum, and comparison of antibody detection assays. J Neurol Sci. 2020;410:116673. [Crossref]
10. Barkhof F, Filippi M, Miller DH, Scheltens P, Campi A, Polman CH, et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain. 1997;120:2059–2069. [Crossref]
11. Cantó LN, Boscá SC, Vicente CA, Gil-Perontín S, Pérez-Miralles F, Villalba JC, et al. Brain atrophy in relapsing optic neuritis is associated with crion phenotype. Front Neurol. 2019;10:1157. [Crossref]
12. Petzold A, Woodhall M, Khaleeli Z, Tobin WO, Pittock SJ, Weinshenker BG, et al. Aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies in immune-mediated optic neuritis at long-term follow-up. J Neurol Neurosurg Psychiatry. 2019;90:1021–1026. [Crossref]
13. Tüzün E, Tzartos J, Ekizoğlu E, Stergiou C, Zisimopoulou P, Coban A, et al. Aquaporin-1 antibody in neuromyelitis optical patients. Eur Neurol. 2014;72:271–272. [Crossref]
14. Şen M, Akbayır E, Mercan Ö, Arsoy E, Gencer M, Yılmaz V, et al. Cytokine-chemokine and cognitive profile of multiple sclerosis patients with predominant optic nerve and spinal cord involvement. J Spinal Cord Med. 2021;44:411–417. [Crossref]

15. Karaaslan Z, Şengül-Yediel B, Yüceer-Korkmaz H, Şanlı E, Gezen-Ak D, Dursun E, et al. Chloride intracellular channel protein-1 (CLIC1) antibody in multiple sclerosis patients with predominant optic nerve and spinal cord involvement. Mult Scler Relat Disord. 2023;78:104940. [Crossref]
16. Erdağ E, Emekli AS, Gündüz T, Küçükali Cİ, Kürtüncü M, Tüzün E. Serum IgG of patients with relapsing inflammatory optic neuropathy immunoreacts with Sox2-positive glial cells of the optic nerve. Mult Scler Relat Disord. 2023;73:104694. [Crossref]
17. Türkoğlu R, Lassmann H, Aker FV, Tzartos J, Tzartos S, Tüzün E. Recurrent tumefactive demyelinating lesions: a pathological study. Clin Neuropathol. 2017;36:195–198. [Crossref]
18. Pechlivanidou M, Xenou K, Tzanetakos D, Koutsos E, Stergiou C, Andreadou E, et al. Potential role of antibodies against aquaporin-1 in patients with central nervous system demyelination. Int J Mol Sci. 2023;24:12982. [Crossref]