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Cerebrospinal 14-3-3 Protein Levels as a Neuroaxonal Biomarker in Aquaporin-4 Antibody–Positive Neuromyelitis Optica Spectrum Disorder

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Abstract

Background and Objectives

To investigate whether CSF 14-3-3 protein levels discriminate aquaporin-4 antibody–positive neuromyelitis optica spectrum disorder (AQP4-NMOSD) from myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) and multiple sclerosis (MS) and the association of CSF 14-3-3 protein levels with clinical features in patients with AQP4-NMOSD.

Methods

This was a multicentric retrospective cohort study of patients with AQP4-NMOSD, MOGAD, and MS, with available CSF samples. 14-3-3 protein levels were quantified using ELISA and compared between the 3 conditions. In patients with AQP4-NMOSD, the association between CSF 14-3-3 protein levels and disability outcomes was explored.

Results

A total of 134 patients were included (AQP4-NMOSD, n = 29; MOGAD, n = 43; MS, n = 62). Patients with AQP4-NMOSD had higher 14-3-3 protein levels (median [interquartile range] 4,441.37 [3,240.05–11526.41] arbitrary units (AU)/mL) compared with those with MS (3,169.86 [2,522.65–3,748.57], $p = 0.001$) and MOGAD (3,112.95 [2,367.37–3,889.43], $p = 0.004$). Patients with AQP4-NMOSD presenting with optic neuritis had lower 14-3-3 levels compared with those with other phenotypes ($p < 0.001$). In AQP4-NMOSD, 14-3-3 levels associated with Expanded Disability Status Scale (EDSS) at attack (β [95%CI] 0.33 [0.15–0.52], $p = 0.003$) and predicted final EDSS ≥ 6.0 (odds ratio 9.48 [1.69; 194.34]; $p = 0.041$) in patients with myelitis.

Discussion

The study suggests a potential role of CSF 14-3-3 protein levels as a biomarker of neuroaxonal damage in AQP4-NMOSD, because of its ability to correlate with disease severity and predict poor clinical recovery.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Supplementary Material

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Classification of Evidence

This study provides Class IV evidence that in individuals presenting with acute myelitis, CSF 14-3-3 differentiates AQP4-NMOSD from MS or MOGAD with a sensitivity of 0.60 (0.30–0.80) and specificity of 0.95 (0.84–1.00).

Introduction

Multiple sclerosis (MS), myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD), and aquaporin-4 seropositive neuromyelitis optica spectrum disorder (AQP4-NMOSD) are the main demyelinating disorders of the CNS identified thus far.[1] Despite their overlapping presentations, AQP4-NMOSD often shows poorer recovery and a more disabling disease course,[2,3] likely because of greater acute neuroaxonal damage.[1] However, studies comparing neurofilament light chain (NfL) between these conditions have yielded discordant results, and other biomarkers of neuroaxonal damage are lacking.[4-6]

14-3-3 is a protein that is abundant in the brain, cytoplasm of neurons, and glia and accumulates in the CSF of patients with severe neuronal damage. CSF 14-3-3 protein detection by immunoblot is highly sensitive and specific for the diagnosis of Creutzfeldt-Jakob disease[7] but also a predictor of conversion to MS and disability in patients with clinically isolated syndrome.[8,9] However, the role of 14-3-3 protein as a biomarker of neuroaxonal damage in other neuroinflammatory disorders has not yet been explored.

The primary aim of this study was to evaluate whether CSF 14-3-3 protein levels differ between AQP4-NMOSD, MOGAD, and MS and to assess the potential diagnostic and prognostic value of this biomarker in patients with AQP4-NMOSD.

Methods

This was a multicentric retrospective cohort study conducted in 5 European centers (Barcelona-Cemcat; Barcelona-Hospital Clinic; Girona-Hospital Dr. Josep Trueta; Verona-University Hospital; Münster-University Hospital) including adult patients with AQP4-NMOSD, MOGAD, and relapsing-remitting MS fulfilling the most recent diagnostic criteria for each disease at the time of recruitment (December 2022).[10-12] Patient selection was based on the availability of CSF samples. Clinical data at attacks and last follow-up and laboratory and radiologic information of the first event was collected.

CSF samples were obtained by lumbar puncture for routine CSF diagnostics, centrifuged to remove cells, and stored at −80°C until used. Samples collected within 3 months from the first attack or subsequent relapses were considered as acute. Otherwise, they were considered as remission. 14-3-3 protein measurement and statistical analyses are described in eMethods.

Standard Protocol Approvals, Registrations, and Patient Consents

This study received approval from the Clinical Research Ethics Committee at Vall d'Hebron University Hospital (EPA [AG] 57/2013 [3,834], PR [AG] 400/2021). All patients signed written informed consents.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

The study included 134 patients (AQP4-NMOSD, n = 29; MOGAD, n = 43; MS, n = 62), all of whom underwent CSF assessment of 14-3-3 protein. Demographic and clinical information is summarized in the Table. Patients with AQP4-NMOSD were older at sampling ($p < 0.001$), presented more frequently with myelitis ($p = 0.002$), and displayed a higher Expanded Disability Status Scale (EDSS) during attacks ($p < 0.001$).

CSF levels of 14-3-3 protein were higher in patients with AQP4-NMOSD (median interquartile range [IQR] 4,471 [3,323–12303] AU/mL) compared with those with MS (3,170 [2,523–3,749], p-adjusted = 0.001) and MOGAD (3,112 [2,358–3,875], p-adjusted = 0.004). No significant differences were found between patients with MOGAD and MS (p-adjusted = 0.989; Figure 1A). Patients with AQP4-NMOSD presenting with myelitis (n = 15) had higher CSF levels of 14-3-3 protein compared with optic neuritis (ON) (n = 9) (12,303 [4,795–17202] vs 3,357 [2,893–3,834], respectively), $p < 0.001$. Within MOGAD and MS groups, the CSF levels were comparable across different phenotypes. A subanalysis focusing on myelitis attacks revealed higher CSF levels of 14-3-3 protein in AQP4-NMOSD compared with MOGAD and MS ($p < 0.001$). Within ON presentations, no differences were found between the 3 conditions (Figure 1B). No significant differences were found between acute and remission phases within each disease group (Figure 1C).

Receiver operating characteristic curve analysis showed good performance of 14-3-3 protein for discriminating patients with AQP4-NMOSD myelitis (n = 15) from both MS (n = 13) and MOGAD myelitis (n = 6) with sampling at the acute phase (area under the curve 0.85 [95%CI 0.72–0.98]; cutoff 8,311.6 AU/mL, sensitivity 0.60 [0.33–0.80], specificity 0.95 [0.84–1.00]) (Figure 1D).

Table Demographic and Clinical Characteristics of Patients With AQP4-NMOSD, MOGAD, and MS

Variables	AQP4-NMOSD N = 29	MOGAD N = 43	MS N = 62	*p* Value
Age at onset, median (IQR)	46.1 (31.8; 56.6)	34.9 (26.7; 45.8)	30.8 (25.4; 39.7)	0.001
Age at sampling, median (IQR)	49.5 (37.3; 59.9)	35.0 (27.9; 47.1)	30.9 (26.1; 39.8)	<0.001
Sex female, n (%)	26 (89.7)	34 (79.1)	46 (74.2)	0.240
Phenotype at acute sampling, n (%)				<0.001
ON	9/24 (37.5)	22/38 (57.9)	16/42 (38.1)	
Myelitis	15/24 (62.5)	6/38 (15.8)	13/42 (31.0)	
Brainstem syndrome	0 (0.0)	0 (0.0)	9 (21.4)	
Other	0 (0.0)	10/38 (26.3)	4/42 (9.5)	
EDSS at acute sampling[a], median (IQR)	4.00 (3.00; 7.00)	3.00 (2.00; 3.88)	2.00 (2.00; 3.00)	<0.001
Time first attack-sampling, d; median (IQR)	91.0 (32.0; 752)	20.0 (1.5; 46.5)	45.5 (16.2; 108)	<0.001
Disease phase at sampling, n (%)				0.011
Acute	26 (89.7)	38 (88.4)	42 (67.7)	
Remission	3 (10.3)	5 (11.6)	20 (32.3)	
Chronic treatment at sampling, n (%)	3/29 (10.3)	1/43 (2.3)	0 (0.0)	0.024
Chronic treatment at any time, n (%)	23/26 (88.5)	17/34 (50.0)	37/102 (59.7)	0.007
Relapsing course, n (%)	19 (76.0)	10/36 (27.8)	41/62 (66.1)	<0.001
Number of relapses after sampling, median (IQR)	0.0 (0.0; 4.25)	0.0 (0.0; 0.5)	1.0 (0.0; 3.0)	<0.001
EDSS at last follow-up, median (IQR)	4.00 (2.00; 7.50)	1.00 (0.00–2.00)	1.50 (1.00–2.00)	<0.001
Follow-up duration, median (IQR) y	4.2 (2.0; 9.5)	1.25 (0.4; 4.1)	19.3 (5.3; 21.1)	<0.001

Abbreviations: AQP4-NMOSD = aquaporin-4 antibody–positive neuromyelitis optica spectrum disorder; EDSS = Expanded Disability Status Scale; IQR = interquartile range; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; MS = multiple sclerosis; ON = optic neuritis.
Comparison analyses were performed using Kruskal-Wallis test for quantitative variables and χ^2 test for qualitative variables.
[a] Additional missing values: AQP4-NMOSD, n = 10; MOGAD, n = 13; MS, n = 21.

In patients with AQP4-NMOSD, CSF 14-3-3 protein levels were associated with age at sampling (β [CI] 0.03 [0.02; 0.05], $p < 0.001$) and EDSS at sampling during attacks (n = 18) (0.28 [0.13; 0.44], $p = 0.001$) (Figure 2A). No other baseline features were significantly associated with 14-3-3 protein levels (data not shown).

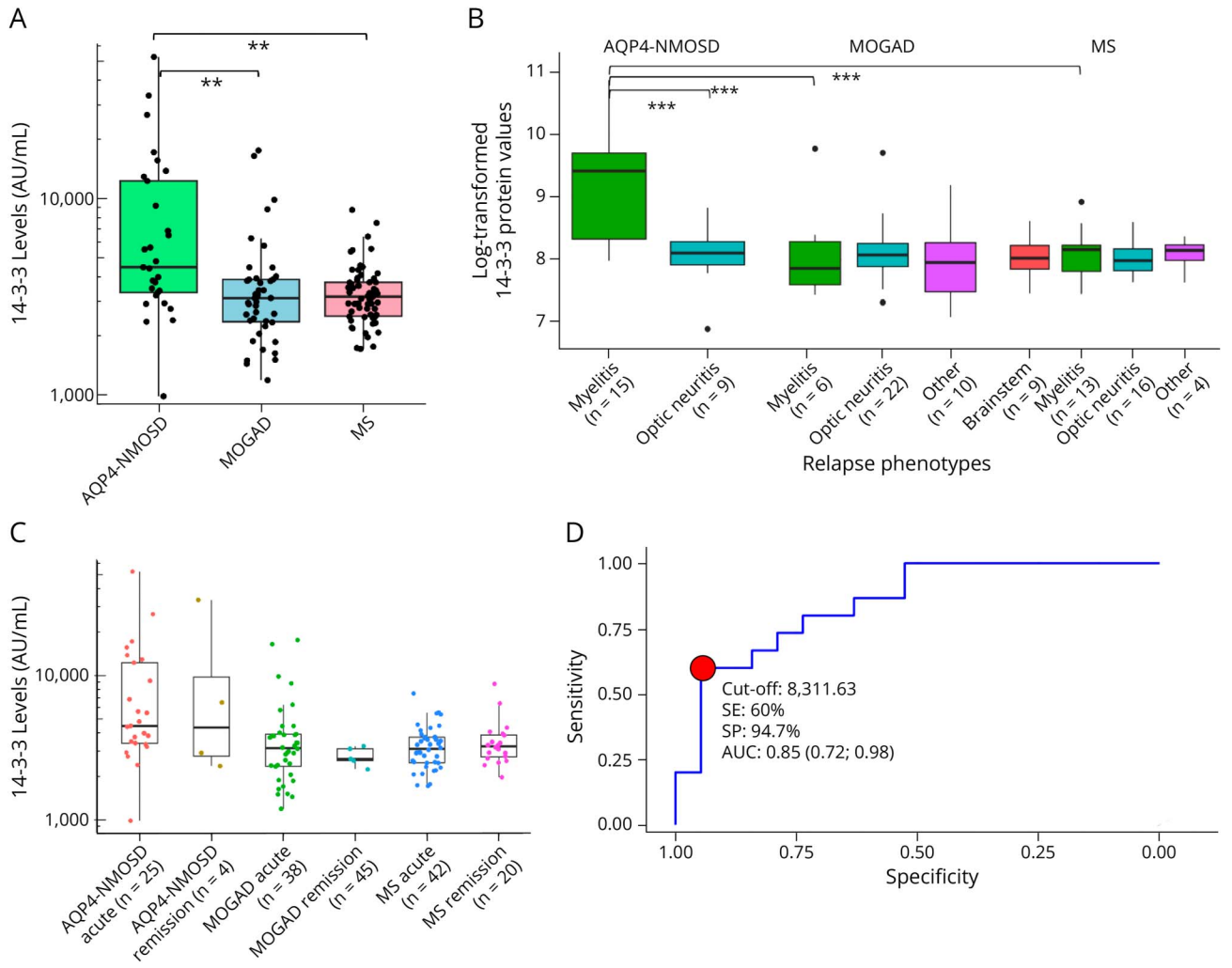
Regarding final disability outcomes, patients with AQP4-NMOSD reaching a final EDSS ≥ 6.0 (n = 11) had higher baseline CSF 14-3-3 protein levels compared with patients with a final EDSS < 6.0 (n = 18) (median [IQR] 12,303.35 [6,067.55–21,932.24] vs 3,391.44 [2,829.43–4,226.36], respectively; p-adjusted = 0.003) (Figure 2B). Similar results were observed when selecting patients with AQP4-NMOSD with sampling at the first attack (EDSS ≥ 6.0, n = 7; EDSS < 6.0, n = 8; p-adjusted = 0.022). In the logistic regression model, 14-3-3 levels predicted final EDSS ≥ 6.0 in the univariate analysis (OR [CI] 10.41 [2.63; 81.12]; $p < 0.001$) but lost significance after adjustment for age and EDSS at sampling and number of relapses after sampling ($p = 0.687$). Among patients with myelitis, 14-3-3 protein predicted this outcome after adjustment by chronic treatment (OR 9.48 [1.69; 194.34]; $p = 0.041$).Regarding relapses, no significant association was found between CSF 14-3-3 protein levels and the annualized relapse rate (β −0.02 [-0.57, 0.53], $p = 0.932$).

Discussion

In this multicentric cohort study, we explored the role of the CSF 14-3-3 protein in AQP4-NMOSD. We found that patients with AQP4-NMOSD displayed higher CSF 14-3-3 protein levels compared with patients with MS and MOGAD, specifically in myelitis and regardless of clinical severity. Furthermore, in patients with AQP4-NMOSD, 14-3-3 protein levels were associated with attack severity and predicted final disability in patients with myelitis.

The discovery of biomarkers such as NfL and glial fibrillary acidic protein (GFAP) has improved our understanding of neurologic conditions, particularly MS.[13] While GFAP has emerged as an important biomarker for AQP4-NMOSD, studies on neuroaxonal markers like NfL have yielded inconsistent results, and its role in predicting outcomes remains

Figure 1 Potential of CSF 14-3-3 Levels for Discriminating Between Patients With AQP4-NMOSD, MOGAD, and MS



Boxplots depict the distribution of CSF levels of 14-3-3 protein between patients with AQP4-NMOSD, MOGAD and MS (A), between phenotypes within each disease and across diseases groups (B), and between acute and remission phases (C). Median values are represented by the horizontal bar, IQR by hinges, 1.5 × IQR by whiskers, and individual values by dots. *p* values are adjusted for age, EDSS, and topography at sampling, and represented by asterisks as follows: **<0.01, ***<0.001. Panel D depicts receiver operating characteristic curves of 14-3-3 protein for the discrimination between patients with AQP4-NMOSD and MS and MOGAD myelitis. Red dot indicates the best cutoff value of 14-3-3 protein. AQP4-NMOSD = aquaporin-4 antibody–positive neuromyelitis optica spectrum disorder; AUC = area under the curve; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; MS = multiple sclerosis; SE = sensitivity; SP = specificity.

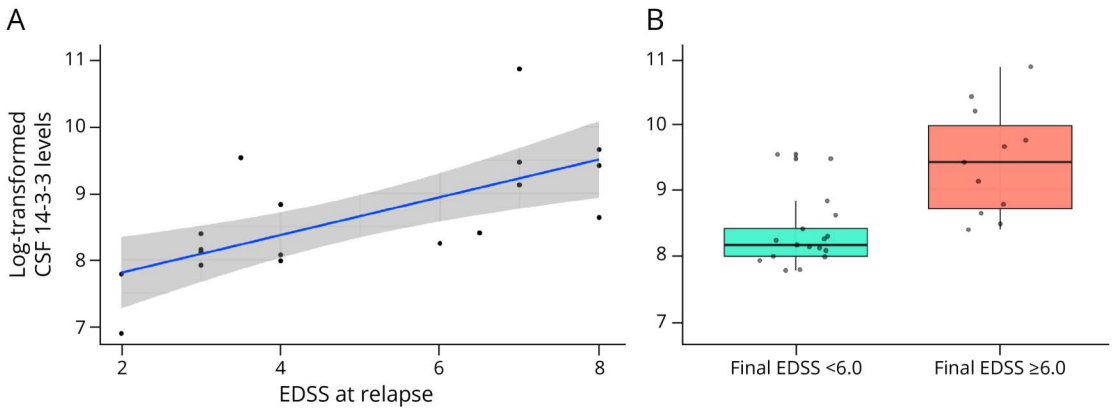
unclear.[4-6,14,15] Therefore, exploring new biomarkers of neuroaxonal damage in AQP4-NMOSD is of utmost importance.

14-3-3 gamma protein is an attractive candidate because of its expression in the cell body and processes of neurons. Detection of the 14-3-3 protein in the CSF by qualitative techniques (i.e., immunoblot) has been associated with disorders that cause severe neuronal damage, notably Creutzfeldt-Jakob disease, but also other conditions such as MS or paraneoplastic neurologic syndromes.[7-9,16,17]

The CSF 14-3-3 protein levels measured by a quantitative immunoassay (ELISA) were elevated in patients with AQP4-NMOSD compared with those with MS and MOGAD, specifically in myelitis presentations and regardless of the severity of the attack. This finding likely reflects secondary neuronal injury due to astrocyte damage, as demonstrated in experimental models,[18] and aligns with data from histopathologic studies showing the relative preservation of neurons and axons in MOGAD and MS compared with AQP4-NMOSD.[1,3] The absence of differences in CSF levels between diseases when selecting ON presentations could be related to the lesser extent of neuroaxonal damage or the lower contact with the CSF of this structure compared with other topographies, hampering the discriminator potential of the protein.

In our study, the CSF levels of 14-3-3 protein associated with the EDSS score at attack and predicted final EDSS ≥ 6.0 in AQP4-NMOSD patients with myelitis, reflecting a more aggressive presentation and poor clinical recovery over disease course. This is in line with some studies reporting higher

Figure 2 Association of 14-3-3 CSF Levels With Disability at Attack and at Last Follow-Up in Patients With AQP4-NMOSD



Panel A represents the association between CSF 14-3-3 protein log-transformed values and EDSS at attack in those patients with samples collected at the acute phase. Boxplots (B) depict the distribution of the 14-3-3 protein log-transformed values between patients with final EDSS ≥ 6.0 and those with final EDSS < 6.0. *p* Values are adjusted for age, EDSS, and phenotype at sampling and represented by asterisks as follows: **<0.01. EDSS = Expanded Disability Status Scale; *AQP4-NMOSD* = aquaporin-4 antibody–positive neuromyelitis optica spectrum disorder.

disability in patients with MS and with acute transverse myelitis of diverse etiologies when the 14-3-3 protein was found in the CSF.[8,9,17]

While serum GFAP is a well-established astroglial biomarker for diagnosing and predicting relapses in AQP4-NMOSD, with the advantage of noninvasive sampling, CSF 14-3-3 may provide complementary diagnostic and prognostic value. However, its moderate sensitivity (60%) for disease discrimination and lack of association with relapse risk limit its stand-alone clinical utility, reinforcing the need for a multibiomarker approach. Clinically, serum GFAP could facilitate early AQP4-NMOSD diagnosis and relapse prediction, optimizing maintenance therapy decisions. Meanwhile, CSF 14-3-3, because of its high specificity, may aid in differential diagnosis in ambiguous cases, particularly in myelitis. Furthermore, its association with long-term disability suggests that it could help identify patients at higher risk of poor recovery after a myelitis attack, supporting the need for more intensive acute treatment or adjustments in long-term therapy. This combined approach could enhance diagnostic accuracy and support personalized treatment strategies.

14-3-3 levels were comparable between MS and MOGAD, likely because of a similar degree of neuroaxonal damage, limiting its utility for distinguishing these conditions. Alternative biomarkers directly related to disease-specific pathophysiology, such as complement factors and cytokines, may offer better diagnostic precision as recently reported.[19,20] Future studies including diverse myelitis etiologies could further elucidate the specificity of 14-3-3 protein. Other limitations of the study include its retrospective design and the lack of longitudinal assessment because of the intrinsic difficulties in accessing CSF samples.

In conclusion, our results support the use of the 14-3-3 protein in CSF as a biomarker of neuroaxonal damage in patients with AQP4-NMOSD and its potential utility in predicting prognosis in these patients.

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Author Contributions

J. Villacieros-Álvarez: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M. Sepulveda: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. A. Valls-Carbó: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. N. Fissolo: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A. Dinoto: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. V. Fernández: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. A. Vilaseca: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. G. Arrambide: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. L. Gutierrez: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M. Castillo: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. L. Bollo: drafting/revision of the manuscript for content, including medical writing for content; major role in

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