Aquaporin-4 Serostatus and Visual Outcomes in Clinically Isolated Acute Optic Neuritis

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Background: Aquaporin-4 antibodies (AQP4-Ab) are associated with neuromyelitis optica spectrum disorder (NMOSD) and typically this disorder has a poor visual prognosis as a result of optic neuritis (ON). Our aim was to report the clinical features at onset and final visual outcomes at 6 months of patients with ON who were positive for AQP4-Ab vs. those who were negative for AQP4-Ab.

Methods: Retrospective cohort study. AQP4-Ab were tested by indirect immunofluorescence in 57 patients with a first episode of ON. All patients initially were referred for consideration of multiple sclerosis ON (MSON), NMOSD, or any other inflammatory central nervous system disorder during follow-up (41.31 ± 24.32 months). Our patients were diagnosed as having NMOSD, MSON, chronic relapsing inflammatory ON, and single isolated ON. Risk factors associated with visual outcomes of ON patients were assessed through an ordinal regression model.

Results: Positive AQP4-Ab were associated with male sex (P = 0.02), earlier age of onset (P = 0.01), and myelitis relapses (P = 0.04). Seronegative group had fewer recurrences of ON than the seropositive group (35% vs 58%, P = 0.14). Patients that were positive for AQP4-Ab did not have worse visual acuity at baseline and after 6 months. However, poor visual acuity during first attack was associated with a worse visual acuity at 6 months (odds ratio = 2.28, 95% CI [1.58–3.28], P = 0.03).

Conclusions: At 6 months, positive AQP4-Ab vs negative AQP4-Ab patients no evidence of poorer visual acuity. Lower visual acuity at baseline was associated with poor visual recovery at 6 months.

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The authors report no conflicts of interest.

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Neuromyelitis optica spectrum disorder (NMOSD) is classified as an astrocytopathy often characterized by devastating neurological sequelae (1,2). Although this disorder classically affects optic nerve and spinal cord, a report of the International Consensus Diagnostic Criteria for NMOSD (IPND 2015) included a range of clinical phenotypes (3). Although detection of aquaporin-4 antibodies (AQP4-Ab) is not an absolute requirement for the diagnosis of NMOSD, they are rarely found in healthy individuals or patients with other inflammatory central nervous system (CNS) disorders (4–6). Although monophasic or recurrent optic neuritis (ON) is a core clinical characteristic of NMOSD, at disease onset the clinician is confronted with a broad range of etiologies. Establishing the correct diagnosis is essential to implement appropriate treatment to give the patient the best possible visual outcome.

The aim of our study was to report in a cohort of Argentinian patients with ON, the clinical features at onset, and final vision at 6 months of those who were positive for AQP4-Ab (P-ON) vs those who were negative for AQP4-Ab (N-ON) or having other causes of ON.

METHODS

Patients from Buenos Aires, Argentina, diagnosed with a first episode on ON (clinically isolated acute ON) were enrolled. A total of 57 consecutive patients who visited the Department of Neurology and Neuro-opthalmology for possible CNS inflammatory disease, without evidence of a metabolic, toxic, infectious, hereditary, vascular, or compressive etiology, between

2009 and 2015 were tested for AQP4-Ab. Ultimate diagnostic categories included AQP4-Ab–positive NMOSD-ON (P-NMOSD-ON), AQP4-Ab–negative NMOSD-ON (N-NMOSD-ON), multiple sclerosis ON (MSON), chronic relapsing inflammatory ON (CRION), single isolated ON (SION), and other causes (7). AQP4-Ab–positive or AQP4-Ab–negative NMOSD was defined according to the International Consensus Diagnostic Criteria (3). ON was defined as visual loss and at least 2 of the following criteria: relative afferent pupillary defect, color desaturation, pain on eye movement, abnormal visual evoked response, and visual field defect (8,9). All patients were evaluated by at least one neurologist and/or one ophthalmologist during and after the first attack. Visual acuity impairment was assessed at baseline and after 6 months in each eye by an ordinal scale according to Wingerchuck et al (10): 0 = normal; 1 = scotoma but visual acuity better than 20/30; 2 = visual acuity of 20/30–20/59; 3 = visual acuity of 20/60–20/199; 4 = visual acuity of 20/200–20/800; 5 = counting fingers only; 6 = light perception; and 7 = no light perception and its equivalent on logarithm of the minimum angle of resolution (LogMAR). The final visual outcomes for bilateral ON (BON) were based on the eye with worse visual acuity at 6 months. Visual impairment was defined as mild (scale: 0–2 or ≤0.4 LogMAR), moderate-severe (scale: 3–4 or from 0.5 to 1.9 LogMAR), and very severe (scale: 5–7 or ≥2 LogMAR). Patients with light perception or no light perception (6–7 on Wingerchuck scale) were excluded from the LogMAR analysis. Patient evaluation included brain (coronal, axial, and sagittal) and spinal cord (axial and sagittal) magnetic resonance imaging (MRI) performed on a 1.5-T scanner. Cerebrospinal fluid analysis included testing for oligoclonal bands (evaluated by isoelectric focusing), whereas a tissue-based indirect immunofluorescence (IIF) technique was used to detect AQP4-Ab (1,11). Positive antinuclear antibodies (ANAs, IIF using Hep-2 Cell culture) were defined as ≥1:160. Other diagnostic tests were performed according to clinical suspicion for a specific diagnosis. All patients were treated with intravenous methylprednisolone (1 g/d) for 3 days during the initial episode of ON.

Statistical Analysis

Statistical analysis was performed using Statistical Program for Social Sciences (SPSS) (version 22.0) and Graph-Pad Prism 6 software. We performed 2 sample *t* tests or the Mann–Whitney U-tests for continuous data and Fisher exact test or χ^2 test for categorical data for the comparisons of P-ON vs N-ON patients, when appropriate. For ordinal regression (cumulative logit model), the whole cohort was evaluated according to Wingerchuck score where 7 is the lowest visual acuity level and 0 represents the highest visual acuity level. At 6 months, we applied a multivariate analysis to assess the impact of different factors (AQP4-Ab status, age at onset, recurrence of ON, unilateral or BON at onset, Winguerchuck score at recovery from first ON attack, and immunosuppressive therapy) on final visual outcomes. The Kruskal–Wallis test (non-parametric test) was used to estimate differences between more than 2 groups (etiological subgroups), and the post hoc analysis was performed using Dunn multiple comparison tests, when appropriate. For all the analyses, the significance level was established as $P < 0.05$.

RESULTS

A total of 57 patients were included. The demographic, clinical, serologic, and MRI features of P-ON vs N-ON patients are summarized in Table 1. The frequency of AQP4-Ab positivity in our patient cohort was 29.82%, P-ON was only found in patients with NMOSD. N-ON group included MSON (n = 14, 24.56%), N-NMOSD-ON (n = 5, 8.77%), CRION (n = 5, 8.77%), SION (n = 8, 14.03%), and others (antiphospholipid syndrome ON [n = 3, 5.26%], Sjögren syndrome ON [n = 2, 3.50%], neurosarcoidosis ON [n = 2, 3.50%], and rheumatoid arthritis ON [n = 1, 1.75%]) (Table 2). At follow-up, we did not find any significant difference between P-ON vs N-ON patients regarding ON relapses, frequency of oligoclonal bands, ANA, and brain MRI lesions. However, longitudinally extensive transverse myelitis (lesions ≥3 spinal segment) on spinal cord MRI was associated with P-ON ($P = 0.04$), and normal spinal cord MRI was associated with N-ON ($P = 0.03$). Although not statistically significant, compared to P-ON patients, we observed that N-ON group had visual acuity 20/40 or better (27.5% vs 11.7%, $P = 0.30$), and was associated with recovery to visual acuity 20/40 or better at 6 months (65% vs 58.8%, $P = 0.76$). In addition, more often P-ON patients had a visual acuity worse than or equal to 20/200 at baseline (76.4% vs 65%, $P = 0.12$) and after 6 months (29.5% vs 27.5%, $P = 0.88$). Forty-one percent of the P-ON group and 27.5% of the N-ON group were excluded from the initial logMAR analysis because they had light perception or no light perception at baseline, and 5.8% in the P-ON group and 12.5% in the N-ON group also were excluded from final logMAR visual acuity for the same reason. The P-ON group had more severe visual loss with initial ON (logMAR VA in P-ON: 1.15 vs VA in N-ON: 0.95, $P = 0.48$) and a worse final visual acuity (final visual acuity in P-ON: 0.51 vs final logMAR visual acuity in N-ON: 0.38, $P = 0.43$). However, none of these trends were statistically significant. Poor visual acuity after the first attack was associated with worse visual acuity at 6 months (odds ratio = 2.28, 95% CI [2.90–15.52], $P = 0.03$) after applying the ordinal regression model (R^2 Nagelkerke = 0.446).

DISCUSSION

In this consecutive cohort of patients with inflammatory ON, seroprevalence of AQP4-Ab was relatively high (29.82%) compared with American and European populations (12,13), but lower compared with Asian population (14). These variations may be due to multiple factors. Ethnic heterogeneity between Asian, Latin American, European, and American populations is likely one factor. In the Asian population, the

TABLE 1. Demographic, serologic status, clinical and MRI features, and final visual outcome of patients with optic neuritis (ON)

	AQP4-Ab (+)	AQP4-Ab (−)	*P* value
No (%)	17 (29.82)	40 (70.18)	
Age at onset, years, m (±SD)	31.58 (±11.10)	38.42 (±12.94)	0.01
Female, No (%)	8 (47.06)	32 (80)	0.02
Bilateral ON (%)	6	12	NS
Unilateral ON (%)	11 (65)	28 (18.18)	
VA at baseline, m (±SD)	4.85 (±1.74)	4.03 (±1.72)	NS
≤2 (mild)	2	11	NS
3–4 (moderate-severe)	4	10	NS
≥5 (very severe)	11	19	NS
LogMAR, m (±SD)	1.15 (±0.25)	0.95 (±0.13)	NS
VA after 6 mo, m (±SD)	2.05 (±2.13)	2.07 (±2.15)	NS
≤2 (mild)	10	26	NS
3–4 (moderate–severe)	4	7	NS
≥5 (very severe)	3	7	NS
LogMAR, m (±SD)	0.51 (±0.17)	0.38 (±0.09)	NS
Recurrence of ON, No (%)	10 (58.82)	14 (35)	NS
No of ON episodes, m (±SD)	1.05 (±1.14)	1.03 (±1.39)	NS
1	4	4	NS
≥2	6	10	NS
Relapses of LETM, No (%)	7 (41.17)	6 (15)	0.04
Relapses of ATM, No (%)	9 (52.94)	11 (27.5)	0.07
No of ATM episodes, m (±SD)	0.29 (±0.68)	0.15 (±0.42)	NS
1	3	4	NS
≥2	2	2	NS
Follow-up years, m (±SD)	4.23 (±1.79)	3.15 (±2.19)	0.04
Paraclinical features			
OCB positive/not available	5/3	10/10	NS
ANA positive/not available	3/2	6/5	NS
Brain MRI			
DIS* (McDonald 2010 criteria)	3	11	NS
Spinal cord MRI			
Normal	6	27	0.03
Partial	2	6	NS
LETM (m of spinal segments)	7 (6.88 ± 7.28)	6 (6.63 ± 3.75)	0.04
LT immunosupressive treatment	17	32	0.08

Spinal cord lesions were defined as follows: partial lesions (only one lesion <3 spinal segments), LETM (lesions ≥3 spinal segments), and normal.

*DIS, dissemination in space (demonstrated by ≥1 T2 lesion in at least 2 of 4 areas of the central nervous system: periventricular, juxtacortical, infratentorial, and spinal cord); ANA, antinuclear antibodies; APQ4-ab, aquoporin-4 antibodies; ATM, acute transverse myelitis; LETM, longitudinally extensive transverse myelitis; LogMAR, logarithm of the minimum angle of resolution; LT, long-term; MRI, magnetic resonance imaging; m, mean; MS, multiple sclerosis; No, number; NS, not significant; OCB, oligoclonal band; SD, standard deviation; VA, visual acuity.

frequency of HLA-DPB1* 0501 is higher (44.9%–73.1%) than in whites (2.6%–5.3%) and in association with AQP4-Ab seropositivity in Han Chinese (15). P-ON was found in 77% of patients with NMOSD, consistent with previously published data where AQP4-Ab detected by IIF was found in 54%–73% of patients with NMOSD (2). Methodology used for detection of AQP4-Ab also is a factor that explains the differences among populations. In our cohort, we acknowledge that only IIF was used for assessment of AQP4-Ab serostatus. This was a limitation of our study given that other reports have shown that a cell-based assay is a more sensitive method (12–16).

We did not find statistically significant differences between P-ON vs N-ON patients with regard to visual acuity at baseline and after 6 months, ON recurrence, oligoclonal band frequency, ANA, and brain MRI lesions. Previous studies have found that P-ON patients are more frequently young, females and have more severe visual acuity loss (7,12,13,16). By contrast, we found a statistically significant association in the P-ON group regarding male sex (P = 0.02) and earlier age of onset (P = 0.01) compared with N-ON patients. Also, P-ON patients had poor visual acuity at onset (4.85 ± 1.74) consistent with previously published data (17).

We found that BON was more frequently observed in the P-ON group compared with the N-ON group. This feature resembles the European more than Asian

TABLE 2. Comparison between subgroups of patients with optic neuritis (ON)

Inflammatory ON	P-NMOSD-ON (n = 17)	N-NMOSD-ON (n = 5)	MSON (n = 14)	CRION (n = 5)	SION (n = 8)	Others* (n = 8)
Age at onset years, m ± SD	31.58 ± 11.10	44.20 ± 9.14	30.85 ± 8.32	41 ± 8.98	33.75 ± 11.92	49.12 ± 17.77
Female, No (%)	8 (47.6)	5 (45.45)	10 (71.43)	5 (100)	4 (50)	7 (87.50)
Unilateral ON at onset	11	3	12	2	5	6
Bilateral ON at onset	6	2	2	3	3	2
VA baseline, m (±SD)	4.85 (±1.74)	5.20 (±1.92)	3.64 (±1.59)	4.70 (±1.71)	2.8 (±1.35)	4.62 (±1.40)
≤2	2	1	4	1	5	—
3–4	4	0	5	1	1	3
≥5	11	4	5	3	2	5
LogMAR, m (±SD)	1.15 (±0.2)	1.15 (±1.2)	0.9 (±0.7)	1.05 (±1.06)	0.7 (±0.7)	1.2 (±0.7)
VA at 6 mo (m ± SD)	2.05 ± 2.13	3.90 ± 1.94	0.96 ± 1.42	2.20 ± 2.86	1.87 ± 1.80	2.75 ± 2.43
≤2	10	0	12	4	6	4
3–4	4	2	2	—	1	2
≥5	3	3	—	1	1	2
LogMAR, m (±SD)	0.5 (±0.1)	0.9 (±0.8)	0.2 (±0.3)	0.1 (±0.1)	0.4 (±0.6)	0.3 (±0.4)
Follow-up years, m (range, yr)	4.23 (2.1–8.3)	4.78 (1–6.9)	5.69 (1.1–7)	3.94 (1–6.6)	2.02 (1–5.5)	1.76 (1–3.6)
Paraclinical features						
OCB in CSF (positive)	5	2	7	1	0	0
AQP4-Ab (positive)	17	0	0	0	0	0
ANA (positive)	3	1	1	2	0	2
MRI finding						
Brain						
McDonald criteria (DIS)	3	0	11	0	0	0
Spinal cord						
LETM	9	5	2	0	0	0
Short lesion	2	0	6	0	0	0
Normal	6	0	6	5	8	8
LT immunosuppressant therapy	17	5	14	5	0	8

*Diagnosis at follow-up: antiphospholipid syndrome (n = 3), Sjögren syndrome (n = 2), neurosarcoidosis (n = 2), and rheumatoid arthritis (n = 1).

ANA, antinuclear antibodies; APQ4-ab, aquoporin-4 antibodies; CRION, chronic relapsing inflammatory ON; CSF, cerebrospinal fluid; DIS, dissemination in space; LETM, longitudinally extensive transverse myelitis; LogMAR, logarithm of the minimum angle of resolution; MSON, multiple sclerosis ON; LT, long-term; NMOSD, neuromyelitis optica spectrum disorder; N-NMOSD-ON, AQP4-Ab-negative NOMSD optic neuritis; OCB, oligoclonal band; P-NMOSD-ON, AQP4-Ab–positive NOMSD optic neuritis; SION, single isolated ON; VA, visual acuity.

population (17,18). There was a trend toward use of immunosuppressant therapy at the first clinical event of ON in the P-ON group.

We are aware of limitations to our study. It was retrospective in design with a limited number of patients, short follow-up period, and possible selection bias. We used IIF to assess AQP4-Ab, and possibly, more patients would have been seropositive using more sensitive methods. Also, myelin oligodendrocyte glycoprotein antibodies are not available at our centers, and this likely affected our diagnostic categories. Both SION and CRION groups might have developed NMOSD, MS, or other systemic disorders if they had a longer follow-up period.

In conclusion, our study adds to the international data set of evaluating P-ON patients. Further prospective and multicenter studies from South America with larger numbers of patients will help expand our initial findings, hopefully leading to more specific diagnostic categories and improved treatment options for patients with ON.

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