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Original article

The relationship between aquaporin-4 antibody status and visual tract integrity in neuromyelitis optica spectrum disorders: A visual evoked potential study

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ABSTRACT

Background: Optic neuritis (ON) is one of the hallmark symptomatic features of neuromyelitis optica spectrum disorders (NMOSD). The majority of patients with NMOSD present highly specific autoantibodies against aquaporin-4 (AQP4). A number of studies have reported poor visual acuity outcomes in individuals with AQP4 seropositive NMOSD, but no such relationship has been found with regard to visual evoked potentials (VEP) parameters such as the amplitude and latency of the P100 component. In this paper, we aimed (i) to describe VEP responses in patients with NMOSD; (ii) to analyze those results based on a scoring system; and (iii) to investigate the association between the VEPs and AQP4 antibody status.

Methods: We retrospectively analysed the VEP responses of 40 patients with a diagnosis of NMOSD (according to the 2015 IPND criteria), including 16 with AQP4-postive status (AQP4[+]) and 24 with AQP4-negative status (AQP4[-]). In the first step, we measured the P100 peak latency and P100-N2 peak-to-peak amplitude in each patient. In the second, we converted these measures to the VEP score (0–10) using the scoring proposed by Jung et al. (2008). All recordings were performed using the same VEP device and testing protocol.

Results: Abnormal VEPs were recorded in 25 of 40 patients (62.6%). Of these, 17 (42.5%) had prolonged P100 latency, and 8 (20%) had no response detected in at least one eye. The patients with ON as the initial relapse symptom had significantly higher median VEP scores than those who experienced the longitudinally extensive transverse myelitis (LETM) at the disease onset (7.0 [interquartile range (IQR), 2.0–8.0] vs. 0.0 [IQR, 0.0–4.0], $p < 0.001$). A lack of VEP response in at least one eye was detected more frequently in the AQP4[+] group than the AQP4[-] group (7/16 vs. 1/24, $p < 0.005$). Logistic regression model controlling for age, gender, disease duration, and the type of relapse at onset showed an independent impact of AQP4[+] status (OR = 35.45, $p = 0.018$) on the higher rate of absent VEP responses. In the entire group of patients ($n = 40$), those with AQP4[+] showed a small tendency towards a higher median VEP score (4.0 [IQR, 0.0–7.8] vs. 1.0 [IQR, 0.0–4.0], $p = 0.304$). Among individuals with abnormal responses ($n = 25$), the patients with AQP4[+] had significantly higher median VEP scores (7.0 [IQR, 4.0–8.5] vs. 3.0 [IQR, 1.0–7.0], $p = 0.034$) and more common bilateral involvement of the optic tracts (80% vs. 40%, $p = 0.048$) than those who were seronegative for anti-AQP4 antibody. A median regression analysis model controlling for age, gender, disease duration, type of onset, and number of relapses in last 12 months showed an independent association between the AQP4-positive status and a higher VEP score in patients with NMOSD ($t = 2.882$, df = 2, $p = 0.007$).

Conclusion: VEP study remains a useful tool in the assessment of NMOSD patients. Due to the high prevalence of absent VEPs in NMOSD patients, the scoring system appears to be more applicable for the precise analysis of VEP recordings. There is a positive association between the AQP-positive serostatus and the poorer outcome in VEP responses, especially in patients with severe impairment of the optic nerve(s).

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1. Introduction

Neuromyelitis optica spectrum disorders (NMOSD) are a group of idiopathic immune-mediated diseases of the central nervous system that are clinically characterized by recurrent episodes of optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM). The pathology of NMOSD involves extensive damage and dysfunction of the astrocytes, resulting in demyelinating lesions (Kawachi and Lassmann, 2017).

In patients with NMOSD, an episode of ON occurs as the initial relapse symptom in 33% of cases, while 80–93% of patients ever develop ON (Asgari et al., 2011; Schmidt et al., 2017). Compared to those with multiple sclerosis (MS), involvement of the optic nerves in NMOSD results in more severe visual impairment and poorer prognoses (Hokari et al., 2016). This is of particular importance because the loss of visual function including both visual acuity and contrast sensitivity has a significant impact on quality of life in patients with NMOSD, specifically those with bilateral or severe optic nerve impairments (Schmidt et al., 2017; Beekman et al., 2019). Loss of visual function contributes to a lesser ability to work or perform daily activities (Schmidt et al., 2017; Beekman et al., 2019). Routinely, the assessment of visual performance comprises the use of a high- and low-contrast letter chart. In the second step, the fundus is examined, which may reveal indicative changes for ON. Despite the easy acceptability of both these measures, there are some important limitations for their use. The visual acuity chart is a subjective measurement, while changes in the fundus are usually absent at the beginning of the optic nerve's inflammation. Thus, for the comprehensive evaluation of the overall visual pathway, visual evoked potential (VEP) study should be considered as it provides an objective measurement of the axonal and demyelinating damage to the visual pathway, including subclinical impairment of the optic nerve (Ringelsteinet al., 2020; Kitley et al., 2014).

The pathognomonic feature of NMOSD is the presence of anti-AQP4 autoantibodies, which are directly involved in the damage of astrocytes with the result of secondary demyelination. The discovery of an autoantibody against AQP4 was a breakthrough moment in defining the criteria for NMOSD, however, seropositive status is not mandatory for the diagnosis of NMOSD. About 20% of patients with NMOSD lack the autoantibodies against AQP4 in the serum (Lennon et al., 2005; Mader et al., 2010; Jarius et al., 2010; Long et al., 2012 ; Waters et al., 2012; Zekeridou et al., 2015; Metz et al., 2016; Vabanesi et al., 2019; Soltys et al., 2019). Of those, about 40% harbor the autoantibody against myelin oligodendrocyte glycoprotein (MOG) (Narayan et al., 2018), and they, compared to AQP4[+] individuals, more commonly experience simultaneous episodes of ON and LETM, yet they tend to recover more quickly and completely than those with AQP-4 autoantibodies. Nearly half remain monophasic after the initial attack (Jarius et al., 2016; Narayan et al., 2018). Importantly, MOG-autoantibody associated diseases comprise a broader clinical spectrum of autoimmune disorders including, along with NMOSD, acute disseminated encephalomyelitis, isolated optic neuritis, myelitis, and encephalitis with epilepsy (Mader et al., 2020).

Multiple studies have examined the impact imposed by the presence of autoantibody against AQP4 on the disease outcome in patients with NMOSD, and a strong correlation has been found between the serological titer and clinical features (including visual acuity), severity, disease activity, stabilization, and prognosis (Siritho et al., 2011; Apiwattanakul et al., 2012; Estiasari et al., 2012; Jarius et al., 2012;Siritho et al., 2014; Sasitorn et al., 2014; Viswanathan et al., 2014; Jarius et al., 2008; Takahashi et al., 2007). In particular, poor visual acuity outcomes have been found in individuals with AQP4-seropositive NMOSD in a meta-analysis by Lin et al., which examined 624 AQP4-positive and 119 AQP4-negative patients. This finding remained significant regardless of the methods of AQP4 detection (Lin et al., 2017;Mekhasingharak et al., 2018).

Among studies exploring the relationship between AQP4 status and VEP measurements, a higher rate of 'unevoked' responses was found among individuals with AQP4-seropositive NMOSD, but none of these studies have found significant differences in the amplitude and latency of the P100 component with regard to AQP4 serostatus (Watanabe et al., 2009; Ringelstein et al., 2014; Ringelstein et al., 2020).

The aims of this study were (i) to describe VEP responses in patients with NMOSD; (ii) to analyze the responses based on a scoring system; and (iii) to investigate the association between the responses and AQP4 antibody status.

2. Methods

2.1. Patients

We retrospectively analysed a group of 40 consecutive patients who were hospitalized at the Neurology Department of Medical University of Warsaw between January 2011 and December 2017 and who met the 2015 IPND criteria of NMOSD (Wingerchuk et al., 2015). We collected demographic and clinical data of the study population for the following parameters: age, gender, disease duration, EDSS score, initial clinical manifestation of the disease, and number of relapses in last 12 months. All enrolled patients underwent laboratory testing for the presence of serum autoantibody against AQP4, which was performed prior to the start of immunomodulatory or immunosuppressant treatment.

2.2. VEP recording

All participants provided a written informed consent prior to the VEP recording. VEPs were recorded in a sound-dampened dark room using silver chloride electrodes with the electrode impedance reduced to less than 5 kΩ at each site. When obtaining the VEP recording, subjects were sitting comfortably with open eyes and were closely monitored for eye movements and alertness.

We performed a monocular stimulation with pattern-reversal black-and-white checks as a stimulus. First, we stimulated the central part of the visual field and then the upper part. A checkerboard pattern was displayed on a video screen that was computer-controlled by a Nicolet Viking machine. VEPs were recorded from an electrode at scalp locations Oz, Oi, O1, and O2 (International 10–20 system) referenced to the Fz electrode, and the ground electrode Fpz. The time-base was 400 ms, and the reversal rate was 1 c/s. A minimum of 2 series of 100 responses were averaged.

We analysed the latency and amplitude of P100 (Pmax.), the N1 and N2 components, and the morphology of the response. The VEP score was calculated by quantifying VEP abnormalities for each side separately according to a six-grade scale (Jung et al., 2008). If both the latency and amplitude of a major EP component were abnormal, the result producing the higher single EP score was taken into account. The worst possible total VEP score was 10 (5 points × 2 sides). See Table 1 for details. The upper limit of the normal P100 latency value was defined as the mean ± 2 SD of latencies obtained from the control group (> 107 ms).

Table 1
The scoring system for the VEP responses (adapted from Jung et al., 2008).

Score	P_{100} latency (ms)
0	Normal
1	pathological side difference of latency
2	latency above the normal range but below 1.1 × upper limit, or >50% side difference of amplitude
3	latency 1.1–1.3 × upper limit
4	latency above 1.3 × upper limit
5	absent P_{100}

In first step, the score is calculated for each eye (0–5), then both scores are summed up (0–10)

2.3. Anti-AQP4 antibody assay

We evaluated the presence of autoantibodies against AQP using indirect immunofluorescence method through commercial fixed cell-based assays (EUROIMMUN, Lübeck, Germany). The serum samples were tested at 1:10, 1:100, 1:1000 dilutions. We used AQP4 transfected and non-transfected HEK4 cells for the incubation process.

2.4. Statistical analysis

We used a student *t*-test and a chi-squared test for cohort characterization. Non-parametric tests (Mann-Whitney or Kruskal-Wallis tests as appropriate) were employed to perform comparisons between the groups for continuous variables, and the chi-squared test was used for the categorical variables. Pearson correlation was applied to test for significant correlations. A multiple logistic regression model was used to determine predictor variables associated with the rate of abnormal and absent VEP responses. It was adjusted to include a binary variable (current ON relapse or not) to exclude its direct impact on the results. In order to investigate the direct relationship between the AQP4-status and the VEP score, we used a median regression analysis model that was controlled for age, gender, disease duration, initial clinical manifestation (ON/LETM), and the number of relapses in the last 12 months. A p-value of 0.05 was considered for statistical significance. Analyses were performed in the software SPSS v26.0 (IBM SPSS Statistics).

3. Results

3.1. Patient characteristics

We enrolled 40 patients in the study, including 16 patients with AQP4-positive serum status (AQP4[+]) and 24 patients with AQP4-negative serum status (AQP4[-]). The mean age was 46.1 (SD ± 11.90) years, and the female-to-male ratio was 4.7. The mean disease duration was 43 (SD+69.92) months. ON was an initial episode in 37.5% of cases. There were no significant differences between the AQP4[+] and AQP4[-] groups with regard to age ($p = 0.284$), gender ($p = 0.126$), disease duration ($p = 0.276$), EDSS ($p = 0.436$), and number of relapses in the last 12 months ($p = 0.316$) (see Table 2 for details).

3.2. General VEP results

Abnormal VEPs were obtained in 25 of the 40 patients (62.6%). Of these, 17 had prolonged VEP latency (42.5%), and 8 had no response (20%) in at least one eye. The patients with absent VEP in at least one eye had significantly higher EDDS scores than patients who had a response in both eyes (4.0 [interquartile range (IQR), 4.0–4.8] vs. 3.5 [IQR, 2.0–4.0], $p = 0.048$).

We found a positive correlation between the disease duration and the P100 latency in the left eye ($r = 0.438$, $p = 0.005$) and the right eye ($r = 0.399$, $p = 0.016$), as well as the mean P100 latency of both eyes ($r = 0.436$, $p = 0.004$). Significant differences in latency between AQP4[+] and AQP4[-] individuals were not found (left, 102 [IQR, 96.3–111] vs. 98.5 [IQR, 93.8–119.0], $p = 0.804$; right, 102 [IQR, 97.3–109] vs. 101 [IQR, 95.3–115], $p = 0.537$). The same was found for amplitude (left, 6.3 [IQR, 4.3–8.5] vs. 7.7 [IQR, 6.7–14.2], $p = 0.062$; right, 7.2 [IQR, 4.8–8.8] vs. 8.2 [IQR, 5.3–12.3], $p = 0.971$) of the P100 component. Abnormal VEP responses were detected more frequently in patients with ON relapse at the disease onset (ON-onset) than in those with LETM (LETM-onset) (93.3% vs. 44%, $p = 0.002$). A lack of stimulated response in at least one eye occurred in 40% of the patients with ON-onset and 8% of those with LETM-onset ($p = 0.014$) (Table 3).

Table 3
Outcomes of VEP responses in patients with NMOSD regarding the initial clinical manifestation and anti-AQP4 antibody status.

	Initial clinical manifestation			anti-AQP4 antibody status		
	ON	LETM	*p-value*	Positive	Negative	*p-value*
LE						
Normal response	4 (19.0%)	17 (81.0%)	0.003*	6 (33.3%)	14 (66.7%)	0.122
Abnormal response	6 (42.9%)	8 (57.1%)		5 (35.7%)	9 (64.3%)	
Absent response	5 (100%)	0 (0%)		4 (80.0%)	1 (20.0%)	
RE						
Normal response	4 (20.0%)	16 (80.0%)	0.057	7 (35.0%)	13 (65.0%)	0.114
Abnormal response	7 (50.0%)	7 (50.0%)		4 (28.6%)	10 (71.4%)	
Absent response	4 (66.7%)	2 (33.3%)		5 (83.3%)	1 (16.7%)	
LRE						
Normal response[1]	1 (6.7%)	14 (93.3%)	0.003*	6 (40.0%)	9 (60.0%)	0.004*
Abnormal response[2]	8 (47.1%)	9 (52.9%)		3 (17.6%)	14 (82.4%)	
Absent response[2]	6 (75.0%)	2 (25.0%)		7 (87.5%)	1 (12.5%)	

AQP4 = aquaporin 4; **ON** = optic neuritis; **LETM** = longitudinally extensive transverse myelitis; **LE** = left eye; **RE** = right eye; **LRE** = left and right eye.
[1] obtained in both eyes.
[2] obtained in at least one eye.
* statistically significant.

3.3. VEP scores

The median VEP score was 2.0 (IQR, 0.0–6.75). There was no association between the median VEP score and demographic factors such as age ($p = 0.454$) and gender ($p = 0.700$).

We found significantly higher VEP scores in ON-onset patients than in those with LETM-onset (7.0 [IQR, 2.0–8.0] vs. 0.0 [IQR, 0.0–4.0], $p < 0.001$).

Table 2
Patients' characteristics.

Characteristics	All patients	Initial clinical manifestation			anti-AQP4 antibody status		
		ON	LETM	*p-value*	positive	negative	*p-value*
Patients, No. (%)	40	15 (37.5%)	25 (62.5%)		16 (40%)	24 (60%)	
Age, mean ± SD	46.1 ± 11.90	43.9 ± 8.41	47.4 ± 13.57	0.319	48.6 ± 13.41	44.5 ± 10.75	0.284
Gender,No. (%)				0.591			0.126
Female	33 (82.5%)	13 (86.7%)	20 (80%)		15 (93.8%)	18 (75.0%)	
Male	7 (17.5%)	2 (13.3%)	5 (20%)		1 (6.3%)	6 (25%)	
Disease duration, mean ± SD	43 ± 69.92	54.9 ± 85.73	36.7 ± 60.22	0.435	27.4 ± 49.39	52.8 ± 79.55	0.276
EDSS, median (Q1, Q3)	4.0 (2.0, 4.9)	4.0 (3.0, 4.0)	4.0 (2.75, 5.75)	0.292	4.0 (3.63, 5.25)	4.0 (2.13, 4.88)	0.436

AQP4 = aquaporin 4; **ON** = optic neuritis; **LETM** = longitudinally extensive transverse myelitis; **EDSS** = Expanded Disability Status Scale.

Table 4
VEP scores in patients with NMOSD regarding the initial clinical manifestation and anti-AQP4 antibody status.

	ON onset (n = 15)	LETM onset (n = 25)	U	p-value	AQP4-postive (n = 25)	AQP4-negative (n = 19)	U	p-value
	The entire group of patients (n = 40)				*The entire group of patients (n = 40)*			
VEP score, median (Q1, Q3)	7.0 (2.0, 8.0)	0.0 (0.0, 4.0)	76.5	0.001*	4.0 (0.0, 7.8)	1.0 (0.0, 4.0)	154	0.304
	Individuals with abnormal response (n = 25)				*Individuals with abnormal response (n = 25)*			
VEP score, median (Q1, Q3)	7.0 (2.0, 8.5)	4.0 (2.0, 6.0)	58.5	0.317	7.0 (4.0, 8.5)	3.0 (1.0, 7.0)	37	0.034*

ON = optic neuritis; **LETM** = longitudinally extensive transverse myelitis; **AQP4-positive** = patients with aquaporin-4-positive NMOSD; **AQP4-negative** = patients with aquaporin-4-negative NMOSD.
* statistically significant.

3.4. AQP4 antibody status

3.4.1. The entire cohort

In the entire group of patients (n = 40), a lack of response in at least one eye after stimulation was detected more frequently in the AQP4[+] group than the AQP4[-] group (7/16 vs. 1/24, $p<0.005$). The AQP4[+] group showed a small tendency towards a higher VEP score (4.0 [IQR, 0.0–7.8] vs. 1.0 [IQR, 0.0–4.0], p = 0.304) and more frequent bilateral involvement of the optic nerves (50% vs. 25%, p = 0.104) than AQP4[-] patients (see Tables 4, 5 and 6).

3.4.2. Individuals with abnormal VEPs

Among the patients with abnormal VEPs (n = 25), there was a significantly higher VEP score in AQP4[+] individuals than those with AQP4[-] status (7 [IQR, 4.0–8.5] vs. 3 [IQR, 1.0–7.0], p = 0.036) (see Tables 4 and 5). Bilateral impairment of the optic nerve occurred more frequently in AQP4[+] patients than those without autoantibodies against AQP4 (80% vs. 40%, p = 0.048) (see Table 6). A threshold of 4.5 score had sensitivity of 70% and specificity of 67% (ROC area under the curve, 0.753) in distinguishing AQP4[+] from AQP[-] patients.

3.4.3. Multiple logistic regression

Among clinical parameters (age, gender, disease duration, type of a relapse at onset) and laboratory parameters (AQP4-status), only the ON-onset was strongly associated with a higher rate of abnormal responses (OR = 18.20, p = 0.011). ON-onset (OR = 21.38, p = 0.026) and AQP4-positive status (OR = 35.45, p = 0.018) were significantly linked to a higher rate of lacking stimulated responses.

3.4.4. Quantile regression model

A median quantile regression analysis controlling for age, gender, disease duration, type of relapse at NMOSD onset, and number of relapses in the last 12 months showed an independent impact of AQP4-positive status on a higher VEP score in the entire group of patients (n = 40) (t = 2.882, p = 0.007) and among the patients with abnormal VEP responses (n = 25) (t = 2.823, p = 0.011).

Table 5
VEP scores in patients with NMOSD regarding the initial clinical manifestation and anti-AQP4 antibody status.

	LETM onset (AQP4-negative) (n = 15)	LETM onset (AQP4-positive) (n = 10)	ON onset (AQP4-negative) (n = 9)	ON onset (AQP4-positive) (n = 6)	p-value
Score, median (Q1, Q3)					
LE	0 (0, 2)	0 (0, 2)	1 (0, 3.5)	5 (2.75, 5.0)	0.003*
RE	0 (0, 1)	0 (0, 2.75)	2 (0, 3.5)	4 (1.5, 5)	0.046*
LRE	0 (0, 4)	0 (0, 4.25)	3 (1, 7)	8 (5.75, 10)	0.005*

LETM = longitudinally extensive transverse myelitis; **ON** = optic neuritis; **AQP4-positive** = patients with aquaporin-4-positive NMOSD; **AQP4-negative** = patients with aquaporin-4-negative NMOSD; **LE** = left eye; **RE** = right eye; **LRE** = left and right eye.
* statistically significant.

4. Discussion

Our data indicate altered VEP responses in the majority of the patients with NMOSD (62.5%). In particular, we found prolonged latency in 42.5% of the patients and absent responses in 20%. These findings are in agreement with a study by Ringelstein et al., where the proportions were 41.9% and 14.0%, respectively (Ringelsteinet al., 2014). In terms of the overall functional status of patients with NMOSD, we found significantly higher EDDS scores in patients with an absent response in at least one eye than those who had responses in both eyes.

As shown in other studies, no significant differences in latency or amplitude of the P100 component were found based on AQP4 serostatus (Watanabe et al., 2009; Ringelstein et al., 2014, 2020). However, we noted a significantly higher prevalence of the absence of response in at least one eye in patients with NMOSD who were AQP4[+] (44%) vs. AQP4[-] (4%). This has also been reported by others (Watanabe et al., 2009; Bukhari et al., 2020; Vabanesi et al., 2019; Neto et al., 2013). We believe that this disproportion of those lacking VEPs after stimulation imposes a major limitation on the analyses of P100 latencies and amplitudes when assessing the impact of risk predictors, given that omitting patients with absent responses could lead to false-positive or false-negative results. Therefore, we applied a scoring system for analyzing VEP recordings in our cohort. To the best of our knowledge, this is the first study to do so.

The median quantile regression model showed an independent association between AQP4-positive status and a poorer outcome of VEPs as measured with the scoring system. The logistic regression model revealed a significant association between AQP4-positive status and a higher rate of absentVEP responses, but no such relationship was found for the rate of abnormal responses. Notably, in a recent longitudinal study by Ringelstein et al., NMOSD patients with no history of ON showed a progressive delay in latency, which was not attributed to serostatus (Ringelstein et al., 2020). In view of this, we suggest that AQP4-positive status results in a worse outcome in VEP responses, which is mainly expressed in patients with severe impairment of the optic nerve.

A higher prevalence of bilateral involvement of visual tracts during ON episodes in AQP4[+] and MOG-positive patients compared to those with MS was reported by Ramanathan et al. (2016). Our data additionally show that bilateral damage to the optic nerves is more common in patients with NMOSD who are AQP4[+] compared to those who are AQP4[-]. Also noted was a similar tendency in the subgroup with subclinical involvement of the visual tracts. Together, an AQP4-positive serostatus along with more severe damage to visual tracts appears to result in a higher risk of bilateral involvement and includes those with no clinical evidence of ON.

Importantly, there are significant differences between MS and NMOSD patients regarding VEPs responses – a predominant demyelinating patterncharacterises MS patients with the occurrence of some

Table 6
The prevalence of bilateral impairment of the optic nerves in VEP study with regard to AQP4 serostatus.

Serostatus	Number of patients with bilateral abnormal responses (%)					
	The entire group of patients (n = 40)	*p-value*	*Subgroup with a history of ON*	*p-value*	*Subgroup without a history of ON*	*p-value*
AQP4[-]	*6/24 (25%)*	*p = 0.104*	*5/11 (46%)*	*p = 0.09*	*1/13 (8%)*	*p = 0.33*
AQP4[+]	*8/16 (50%)*		*6/7 (86%)*		*2/9 (22%)*	
	The patients with abnormal response (n = 25)	*p-value*	*Subgroup with a history of ON*	*p-value*	*Subgroup without a history of ON*	*p-value*
AQP4[-]	*6/15 (40%)*	*p = 0.048**	*3/9 (38%)*	*p = 0.04**	*3/6 (50%)*	*p = 0.64*
AQP4[+]	*8/10 (80%)*		*6/7 (83%)*		*2/3 (67%)*	

AQP4[+] = the group of patients with aquaporin-positive NMOSD; **AQP4[-]** = the group of patients with aquaporin-negative NMOSD; **ON** = optic neuritis.
* statistically significant.

extreme latency delays, while axonopathy is the dominating component in NMOSD as there are more frequent absent responses (Bukhari et al., 2020; Vabanesi et al., 2019; Neto et al., 2013; Ohnari et al., 2016). In contrast to MS, where the prolonged P100 latency may result from the damage at any part of the visual pathway, the abnormal VEP response in NMOSD specifically reflects changes in the optic nerves. This is especially important as the abnormal response in VEP recording may be present prior to the occurrence of an ON episode in patients with NMOSD (Wu et al., 2019). Bearing this in mind, with the VEP study at hand, more effective management can be delivered to these patients.

Because the intraretinal nerve fibers are affected during episodes of ON, optical coherence tomography (OCT) could be complementary to a VEP study for diagnosing and monitoring disease progression (Bennett et al., 2015; Oertel et al., 2017). The patterns in OCT differ between AQP4-NMOSD, MOG-NMOSD, and MS, showing much more expression of thinning retinal fibers and the ganglion cell layer in those with NMOSD (Bennett et al., 2015; Pache et al., 2016; Oertel et al., 2017; Stiebel-Kalish et al., 2017; Sotirchos et al., 2019), and a significantly smaller foveal thickness in patients with LETM-NMOSD compared to healthy controls (Oetel et al., 2017). Interestingly, a combined OCT-VEP index could differentiate patients with NMOSD from those with MS who had experienced an ON episode with 100% accuracy and 88.9% sensitivity (Vabanesi et al., 2019).

5. Limitations

In contrast to other study populations, ours was primarily (60%) seronegative to autoantibodies for AQP4. This could partially be due to the inclusion of individuals with MOG antibodies in our cohort. Importantly, an ON episode in AQP4[+] and MOG-positive patients differs in pathomechanism (astrocytopathy vs. oligodendropathy) as well as the pattern of optic nerve involvement (predominantly the orbital part of the optic nerve and chiasm vs. the orbital, canalicular, and intracranial parts with severe swelling at onset) (Kawachi and Lassmann, 2017; Shen et al., 2019). Therefore, a lack of testing for MOG autoantibodies in the AQP4[-] subgroup could have influenced our results, given that different outcomes are expected between AQP4[-] and MOG-positive patients.

6. Conclusion

In conclusion, the present data indicate that the VEP study is a useful tool in the assessment of patients with NMOSD. Due to the high prevalence of absent VEPs responses in NMOSD patients, the scoring system seems to be more applicable for the precise analysis of VEP recordings than the comparison of P100 latency and amplitude, particularly when investigating the prognostic factors. There is a positive association between AQP-positive serostatus and poorer outcomes in VEP responses, which is predominantly expressed in patients with severe impairment of the optic nerve. Therefore, we suggest that NMOSD patients with AQP4-positive serostatus follow more frequent and profound assessments of the visual pathway integrity in order to provide more satisfactory and effective management for this particular group of patients.

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Declaration of Competing Interest

The authors state no conflict of interest.

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