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Research Article

Neuromyelitis Optica Spectrum Disorder: Epidemiological, Clinical and Prognostic Study in a Tunisian Cohort

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Abstract

Background: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory disorder that affects the central nervous system. This study aimed to characterize the demographic and clinical features of NMOSD in Tunisia and to identify predictive factors for poor outcomes.

Methods: We conducted a retrospective study over four years at the Neurology Department of the National Institute of Neurology, Mongi Ben Hmida, Tunis, including patients diagnosed with NMOSD.

Results: The study included 30 patients with NMOSD, with a mean age of onset of 35.86 ± 13.42 years. There was a notable predominance of females (sex ratio of 1M/9F). Systemic lupus erythematosus was the most common associated autoimmune disorder, occurring in 17% of cases. Myelitis was the primary clinical manifestation, observed in 53% of patients, particularly affecting those over 50 years old (13% of the cohort). The initial presentation of NMOSD was predictive of the type of subsequent neurological event. Magnetic resonance imaging (MRI) identified short-segment myelitis in 17% of patients, while anti-AQP4 antibodies were detected in 77%. Severe disease progression (Expanded Disability Status Scale [EDSS] score ≥ 6) was linked to male sex, significant initial disability (initial EDSS score ≥ 4), and a higher number of relapses.

Conclusion: This study demonstrates the increased risk of severe disease progression in male and elderly patients, especially those with spinal cord involvement, highlighting the critical need for timely NMOSD diagnosis in this population.

Keywords: Neuromyelitis optica spectrum disorder; Aquaporin-4 antibodies; Magnetic resonance imaging; Plasma exchange; Prognosis; Tunisia.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD), previously known as Devic disease, is an autoimmune inflammatory disorder of the central nervous system that can lead to severe disability[1]. Initially, it was uncertain whether neuromyelitis optica represented a distinct disease or simply a more severe form of "optico-spinal" multiple sclerosis (MS)[2]. However, in 2004, the discovery of highly sensitive and specific NMO-specific immunoglobulins (NMO-IgGs) targeting aquaporin 4 (AQP4) in patients with NMOSD clarified their distinction from MS[3]. This finding prompted us to recognize NMOSD as a separate clinical entity.

Although implementation of the International Panel for NMO Diagnosis (IPND) criteria has improved early and accurate diagnosis [1], diagnosing NMOSD remains challenging, particularly in cases lacking AQP4 antibodies. Consequently, there is a need to further understand the clinical features and disease progression of NMOSD, especially in specific populations such as Tunisia. Therefore, the objective of our study was to provide a comprehensive description of the demographic and clinical characteristics of NMOSD within a Tunisian patient cohort, and to identify predictive factors for poor disease outcomes.

By elucidating these aspects of NMOSD in Tunisia, our research aims to provide valuable insights into the understanding and management of this condition, ultimately leading to improved diagnosis, treatment, and prognosis in affected individuals.

2. Patients and Methods

2.1 Study Population

We conducted a retrospective review of the medical records of 30 patients diagnosed with NMOSD who presented 2017 and 2020 to the Neurology Department of the National Institute of Neurology, Mongi Ben Hmida, Tunis (NINT) between 2017 and 2020. Inclusion criteria for the study were patients over 15 years of age who met the 2015 International Diagnostic Criteria for NMOSD [1].

2.2 Data Collection

Demographic, clinical, biological, neuroimaging, and treatment data were collected using dedicated forms. Information was obtained from hospital files and patient interviews. All the patients were tested for anti-AQP4 antibodies using an indirect immunofluorescence assay. However, MOG -serostatus was not assessed in our patient cohort.

The following factors were evaluated: age at onset, sex, disease duration, disease course, type of syndrome (based on the 2015 criteria) at onset and second attack, time to first relapse, cumulative number of relapses, presence of longitudinally extensive myelitis on magnetic resonance imaging (MRI) (lesions extending over three vertebral segments), brain MRI abnormalities at onset and during follow-up, cerebrospinal fluid (CSF) oligoclonal bands (OCB), protein level, cell count, and associated autoimmune diseases. Neurological disability status was assessed using the Expanded Disability Status Scale (EDSS) score.

Relapse was defined as the occurrence of new or worsening acute neurological symptoms lasting ≥24 h that were not attributable to fever, infection, or metabolic conditions [4]. Severe relapse was defined as an EDSS score ≥6.0 at the lowest point of the attack, or an increase of 0.5, if the patient had a baseline EDSS score of ≥6.0 [5]. In cases of optic neuritis (ON), a severe attack persists for at least six months and is characterized by a visual acuity of ≤0.1 persisting for at least six months. Typical optic neuritis was defined as unilateral painful visual loss in a young patient (<50 years old) with a normal or mildly swollen optic disc and good prognosis [6].

The IPND criteria recommend a minimum of five years (preferably longer) of relapse-free clinical observation after the index events to confidently assume a monophasic course [1]. Based on the age at disease onset, we categorized the patients into two subgroups: late-onset neuromyelitis optica spectrum disorder (LO-NMOSD) (onset at ≥50 years) and early -onset neuromyelitis optica spectrum disorder (EO-NMOSD) (onset at <50 years).

2.3 Statistical Analysis

Statistical analysis involved Fisher's exact test for contingency tables, Mann-Whitney U test for comparing continuous data, and Wilcoxon test for comparing paired groups. The Kaplan-Meier method was used to estimate the time to assignment of EDSS scores ≥6, and survival curves were compared using the log-rank test. Cox proportional hazards regression analysis was used to analyze the predictive factors for disability. Statistical significance was set at $p < 0.05$.

2.4 Ethical Considerations

Informed consent was obtained from all patients who were interviewed to ensure adherence to the ethical guidelines.

3. Results

3.1 Demographic and Clinical Data:

During the study period, 30 patients were diagnosed as having NMOSD. The main patient characteristics are summarized in Table 1. The median age at onset was 34 years, and a significant majority of the patients were female (sex ratio=1M:9F). Myelitis was the first clinical event in 43% of the patients. Notably, all patients with late-onset NMOSD (≥50 years) had myelitis as their initial clinical manifestation, whereas only 35% of patients with early onset (<50 years) experienced myelitis.

Among patients with monofocal optic nerve onset, approximately two-thirds presented with typical optic neuritis. The majority of patients (83%) had a relapsing disease course, while 5 patients experienced a single attack during the follow-up period (median follow-up, = 36 months). Only one patient with a long observation period of 72 months was classified as having a monophasic form of the disease, and this patient had the most severe initial disability (EDSS score of 7).

For patients with a relapsing disease, the median annualized relapse rate was 1.16, and myelitis was the most common manifestation at the second attack, occurring in 72% of cases. The initial presentation type had a statistically significant predictive value for a second attack type (Table 2). The median time to first relapse was 12 months, and this time period was inversely correlated with a higher number of attacks during the first year of disease progression (p=0.022).

Table 1. General characteristics, clinical and treatment features of the NMOSD patients.

Data	Values
Gender, *n* (%)	
Male	3(10)
Female	27(90)
Sex ratio	1:9
Age of onset (years)	
Mean ± SD	35.86±13.42
Median	34
Range	15 -71
Distribution, n(%)	
*EO-NMOSD**	26(87)
*LO-NMOSD***	4(13)
Follow-up duration (months)	
Mean ± SD	60±5
Median	36
Range	4 – 216
Time to diagnosis (months)	
Mean ± SD	32.7±43
Median	21
Range	1 – 180
First clinical event, n(%)	
Myelitis	13(43)
ON	11(37)
Brainstem	2(7)
Multifocal	4(13)
Simultaneous ON and myelitis	2(7)

Table 1 continued on the next page..

Disease course, n(%)	
Relapsing	25(83)
Monophasic	1(3)
Insufficient follow up	4(13)
Time to first relapse (months)	
Mean ± SD	15±8
Median	12
Range	1 – 120
Annualized relapse rate	
Mean ± SD	1.78±1.72
Median	1.16
Range	0.11 – 6
Patients receiving DMT, n(%)	25(83)
Time from onset to treatment (months)	
Mean ± SD	17.3±29.7
Median	1.5
Range	0 – 120
Annualized relapse rate after DMT	
Mean ± SD	1.28±1.98
Median	0
Range	0 – 8

DMT: Disease modifying therapy; EO-NMOSD: early-onset neuromyelitis optica spectrum disorder; IST: immunosuppressant; LO-NMOSD: late-onset neuromyelitis optica spectrum disorder; n: number; NMOSD: Neuromyelitis spectrum disorder; ON: Optic neuritis; SD: Standard deviation.

* EO-NMOSD: < 50 years of age at onset.
** LO-NMOSD: ⩾ 50 years of age at onset.

Table 2. Predictive value of the initial presentation for the second attack.

	Concordance	p
Myelitis	61%	<0.001
ON	30%	0.023
BS syndrome	65%	<0.001

BS: Brainstem; ON: Optic Neuritis

3.2 Neuroimaging, Biological, and Neurophysiological Features

The detailed features are summarized in Table 3.

On MRI, 40% of the patients exhibited typical cerebral lesions, 47% had extensive myelitis, and 17% had short myelitis. Among the 13 patients with monofocal spinal cord onset, 38% had short myelitis and 15% showed subclinical optic nerve lesions on initial MRI. Similarly, among patients with monofocal optic nerve onset, 18% had subclinical myelitis on initial spinal cord MRI (Figure 1).

Follow-up MRI was performed in 22 patients, with 23% of these scans being conducted during further attacks. Among the patients with spinal cord atrophy on follow-up MRI (seven patients) within a median time of 12 months (range, 3-168 months), one patient exhibited dorso-lumbar spinal cord atrophy with cervical short myelitis on follow-up MRI, despite having no clinical history of myelitis or any spinal cord lesions on the initial MRI.

The presence of anti-AQP4 antibodies were detected in more than three quarters (77%) of the patients. Notably, in one patient with recurrent optic neuritis, anti-AQP4 antibody positivity was observed only after five years of disease evolution.

Half of the patients with positive antinuclear antibodies (ANA) were diagnosed with associated systemic lupus erythematosus (17% of with NMOSD patients). Among these patients, two had short multifocal myelitis, while the remaining three had typical NMOSD radiological features.

Of the 11 patients who experienced recurrent optic neuritis, 50 episodes were recorded. An analysis of the location of recurrent attacks revealed that 7 out of the 11 patients (64%) had contralateral optic nerve involvement, accounting for 66% of the total episodes.

Table 3. Neuroimaging, biological and neurophysiological features of the NMOSD patients.

Data	Values
Initial brain MRI, n(%)	**30(100)**
Normal	8(27)
Typical brain abnormalities	12(40)
Initial spinal cord MRI, n(%)	**30(100)**
Normal	11(37)
LETM	14(47)
SM	5(17)
Time from initial MRI to follow-up MRI (months)	
Mean ± SD	29.85 ± 43.05
Median	12
Range	[3 - 168]
Follow-up brain MRI, n(%)	**22(73)**
Normal	3(14)
Typical brain abnormalities	14(63)
ON atrophy	6(27)
Follow-up spinal cord MRI, n(%)	**22(73)**
Normal	2(9)
LETM	13(59)
SM	5(23)
SC atrophy	7(32)
Initial CSF results, n(%)	**30(100)**
CSF cell count WC ≥10/μl	12(40)
CSF protein >0.6 g/L	13(43)
OCBs	1(3)
AQP4 seropositive, n(%)	**23(77)**
ANA seropositive, n(%)	**10(33)**
VER on onset, n(%)	**30(100)**
Unilateral demyelinating RBON	10(33)
Bilateral demyelinating RBON	7(23)
Unilateral axonal RBON	3(10)
Bilateral axonal RBON	0(0)
Subclinical RBON	3(10)
Patients having ON relapses during the disease progression	**11(37)**
VER during relapses	
Ipsilateral RBON	4(36)
Contralateral RBON	7(64)

ANA: Antinuclear antibodies; AQP4: aquaporin-4; CSF: Cerebral-spinal fluid; OBS: Oligoclonal bands; ON: Optic nerve; RBON: Retrobulbar optic neuritis; SM: Short myelitis; VER: Visual evoked responses; WC: White cells.
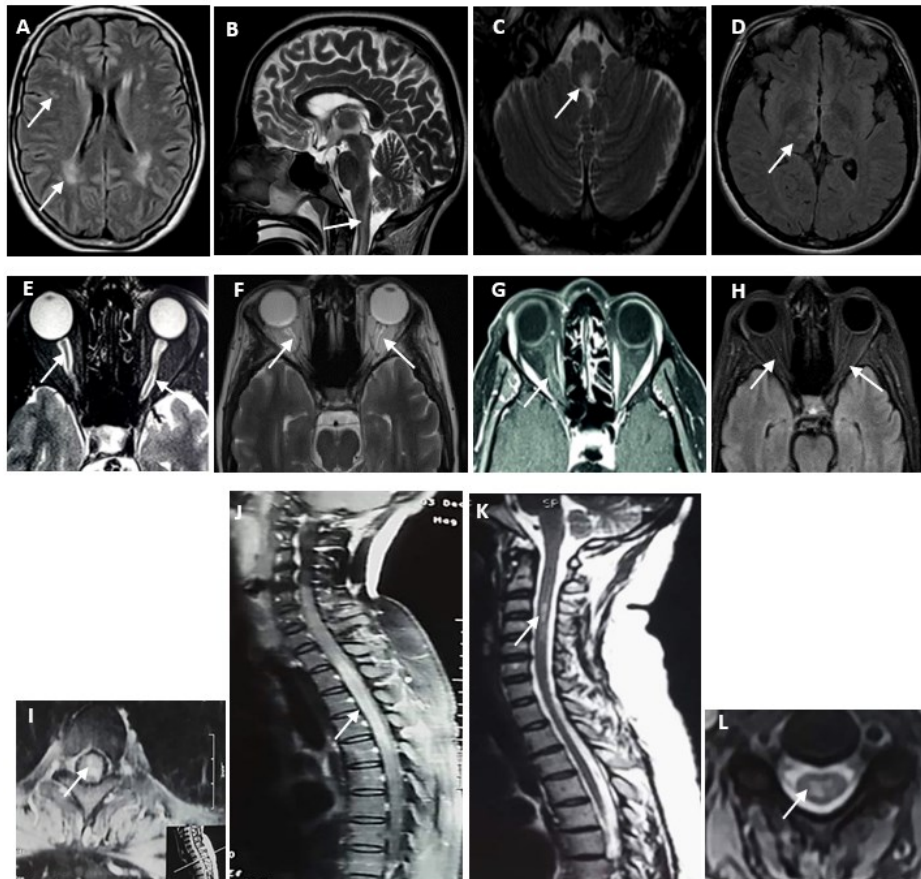
Figure 1. *MRI findings of six NMOSD patients. A, B, C: Brain MRI of a patient with AQP4+ NMOSD and area postrema syndrome demonstrating bilateral subcortical and deep white matter lesions on axial fluid-attenuated inversion recovery (FLAIR) MRI (A) and T2 hyperintensity in the dorsal medulla on T2 weighted brain sagittal MRI (D) with typical symmetrical ependymal lesion around the periaqueductal area on T2 weighted brain axial MRI (C). D: Axial fluid-attenuated inversion recovery (FLAIR) MRI of a patient with AQP4+ NMOSD showing lesions involving the thalamus and the hypothalamus. E, F, G: T2 weighted orbital axial (E) and Short Tau Inversion Recovery (STIR) (F) MRI of a patient with AQP4+ NMOSD and retrobulbar optic neuritis showing bilateral increased T2 and STIR signals within optic nerves with gadolinium enhancement (G). H: Orbital axial FLAIR MRI of a patient with AQP4+ NMOSD and recurrent retrobulbar optic neuritis demonstrating bilateral optic nerve atrophy. I, J: Spine sagittal (I) and axial (J) FLAIR MRI of a patient with AQP4+ NMOSD presenting with spastic paraplegia and urinary retention showing longitudinally extensive myelitis from C5 to D8. K, L: Spine sagittal (K) and axial (L) T2 weighted MRI of a patient with AQP4+ NMOSD presenting only with retrobulbar optic neuritis showing central medullar non-extensive myelitis.*

AQP4, aquaporin 4; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; STIR, Short Tau Inversion Recovery.

3.3 Treatment

During the attacks, all patients received intravenous methylprednisolone pulses lasting 3-10 days, followed by oral corticosteroid therapy. Plasma exchange (PE) or intravenous immunoglobulin (IVIG) is used as an add-on therapy for severe NMOSD. No significant differences were observed between the PE-steroid-treated group and the steroid -treated group in terms of acute and residual EDSS scores, as well as ΔEDSS (acute EDSS-residual EDSS). However, the mean ΔEDSS value was slightly higher in the PE-steroid-treated group than in the control group (Table 4).

Most patients (83%) received disease-modifying therapy (DMT), with azathioprine being the most used agent in 17 patients, followed by mycophenolate mofetil in 6 patients, and cyclophosphamide in 2 patients. The median time to initiation of DMT was 1.5 months, and the median annualized relapse rate decreased from 1.16 to 0 after the initiation of DMT (Table 1).

Table 4. Disability measured as EDSS during attacks in PE-treatment as an add-on versus steroid-only.

	St only	PE-St	p
Mean acute EDSS	2.8	3.4	0.63
Mean residual EDSS	1.8	1.99	0.57
Mean ΔEDSS*	1	1.41	0.59

PE: plasma exchange; EDSS: Expanded Disability Status Scale; St: Steroid.

* ΔEDSS = acute EDSS - residual EDSS.

3.4 Predictive Factors of Disability

In the univariate survival analysis of EDSS, male sex, high cumulative number of attacks, and significant initial disability (initial EDSS score ≥ 4) were found to be significantly predictive of achieving an EDSS score of 6 ($p=0.01$, $p=0.022$, and $p < 0.0001$, respectively). Although patients with late-onset NMOSD (LO-NMOSD), spinal cord onset, positive AQP4 serostatus, and spinal cord atrophy on follow-up MRI tended to have a shorter time to an EDSS score of 6, no statistically significant differences were observed among the different groups ($p=0.511$, $p=0.544$, $p=0.273$, and $p=0.561$, respectively). Patients with positive anti-ANA serostatus tended to have a longer time to reach an EDSS score of 6, but no positive predictive value was identified. Using the Cox proportional hazards model, only a significant initial disability (initial EDSS score ≥ 4) was independently associated with a higher risk of severe disability (EDSS score ≥ 6) ($p=0.045$).

4. Discussion

The implementation of the IPND criteria has enhanced the diagnosis of NMOSD, and this study adds to existing literature by examining prognostic factors among Tunisian patients with NMOSD. The demographic profile of our patients aligns with previous studies, showing a median onset age of 34 years and a higher prevalence in women[1,7,8]. Notably, male patients experienced an earlier onset of disability, echoing findings from a British study[9]. These gender differences may indicate a hormonal influence on the disease's development and progression.

Most individuals in our cohort presented with a relapsing-remitting form of the disease, while a smaller group exhibited a monophasic course over a median follow-up of 36 months. In line with prior research, myelitis was the most frequent initial symptom, followed by optic neuritis. Older patients and those with spinal cord onset were more likely to develop motor disabilities. We observed a negative correlation between the median time to first relapse and the number of attacks within the first year, suggesting that early disease activity could lead to poorer outcomes. Furthermore, the nature of the initial attack served as a predictor for subsequent attacks, with recurrent episodes of optic neuritis affecting the optic nerve irrespective of prior attack locations.

Neuroimaging revealed characteristic cerebral lesions, extensive myelitis, and short myelitis in our patients, consistent with earlier findings[10-12]. Additionally, subclinical optic nerve lesions and myelitis were identified, indicating ongoing disease activity beyond classical attacks. Notably, spinal cord atrophy, particularly in the lumbar region, emerged as a predictor of disability and may serve as a biomarker for disease progression.

Anti-AQP4 antibodies were present in 77% of our cohort, underscoring their significance as diagnostic markers for NMOSD[13]. It is important to note that in one patient with recurrent optic neuritis, anti-AQP4 positivity was only detected five years into the disease, highlighting the possibility of seroconversion over time.

During acute attacks, treatment typically involves corticosteroids, with plasma exchange or intravenous immunoglobulin reserved for severe cases[14,15]. Most patients received disease-modifying therapy (DMT), primarily azathioprine, mycophenolate mofetil, or cyclophosphamide, leading to a reduction in the annual relapse rate. This underscores the importance of early, proactive treatment in improving disease outcomes [16].

Significantly, initial disability was identified as the strongest predictor of disease progression, with an initial EDSS score of ≥4 indicating greater risk. Male sex and a high cumulative attack count were also linked to an increased likelihood of severe disability[9,17]. These findings highlight the critical need for early identification and intervention in patients exhibiting substantial initial disabilities to mitigate disease progression and enhance long-term outcomes.

While our study offers valuable insights into the demographic, clinical, and prognostic characteristics of NMOSD in a Tunisian cohort, it has limitations. The retrospective design and relatively small sample size restricted our capacity for extensive statistical analysis. Additionally, anti-MOG antibodies were not assessed, which could have provided further insights.

Conclusion

In conclusion, the demographic and clinical traits of NMOSD in our patients are consistent with findings from Western studies, and significant initial disability has emerged as a crucial prognostic factor. Future multicenter studies with larger samples are essential to validate our results and investigate additional factors that may influence the disease course and treatment responses in NMOSD.

Conflict of Interest

None declared.

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