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Disease Course and Outcomes in Patients With the Limited Form of Neuromyelitis Optica Spectrum Disorders and Negative AQP4-IgG Serology at Disease Onset: A Prospective Cohort Study

Xiaodong Chen[a]
Jing Zhou[b]
Rui Li[a]
Bingjun Zhang[a]
Yuge Wang[a]
Xiaonan Zhong[a]
Yaqing Shu[a]
Yanyu Chang[a]
Wei Qiu[a]

[a]Department of Neurology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China
[b]Department of Neurology, Foshan First People's Hospital, Foshan, China

Background and Purpose Patients presenting with clinical characteristics that are strongly suggestive of neuromyelitis optica spectrum disorders (NMOSD) have a high risk of developing definite NMOSD in the future. Little is known about the clinical course, treatment, and prognosis of these patients with likely NMOSD at disease onset.

Methods This study prospectively recruited and visited 24 patients with the limited form of NMOSD (LF-NMOSD) at disease onset from November 2012 to June 2021. Their demographics, clinical course, longitudinal aquaporin-4 immunoglobulin G (AQP4-IgG) serology, MRI, therapeutic management, and outcome data were collected and analyzed.

Results The onset age of the cohort was 38.1±12.0 years (mean±standard deviation). The median disease duration was 73.5 months (interquartile range=44.3−117.0 months), and the follow-up period was 54.2±23.8 months. At the end of the last visit, the final diagnosis was categorized into AQP4-IgG-seronegative NMOSD (*n*=16, 66.7%), AQP4-IgG-seropositive NMOSD (*n*=7, 29.2%), or multiple sclerosis (*n*=1, 4.2%). Seven of the 24 patients (29.2%) experienced conversion to AQP4-IgG seropositivity, and the interval from onset to this serological conversion was 37.9±21.9 months. Isolated/mixed area postrema syndrome (APS) was the predominant onset phenotype (37.5%). The patients with isolated/mixed APS onset showed a predilection for conversion to AQP4-IgG seropositivity. All patients experienced a multiphasic disease course, with immunosuppressive therapy reducing the incidence rates of clinical relapse and residual functional disability.

Conclusions Definite NMOSD may be preceded by LF-NMOSD, particularly isolated/mixed APS. Intensive long-term follow-up and attack-prevention immunotherapeutic management is recommended in patients with LF-NMOSD.

Keywords neuromyelitis optica spectrum disorders; anti-aquaporin 4 autoantibody; area postrema; optic neuritis; treatment outcome.

INTRODUCTION

Neuromyelitis optica (NMO) is an autoimmune inflammatory demyelinating disease distinct from multiple sclerosis (MS) that preferentially affects the optic nerve and spinal cord.[1] Detectable serum autoantibodies targeting the astrocytic water channel aquaporin-4 immunoglobulin G (AQP4-IgG) are highly specific pathogenic biomarkers in populations with NMO.[2] The unifying term "neuromyelitis optica spectrum disorders" (NMOSD) was introduced in 2007[3] and expanded in 2015[4] to include patients who fulfill the clinical characteristics and supportive MRI findings despite AQP4-IgG serological negativity. The revised

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Correspondence
Wei Qiu, MD, PhD
Department of Neurology, The Third Affiliated Hospital of Sun Yat-sen University, NO. 600, Tianhe Road, Tianhe District, Guangzhou 510630, Guangdong, China
Tel +8615899968330
Fax +86-20-85252238
E-mail qiuwei120@vip.163.com

International Panel for NMO Diagnosis (IPND) criteria facilitate the early diagnosis of NMOSD, which has further contributed to earlier the initiation of attack-prevention strategies. However, it is quite difficult to establish a diagnosis of NMOSD according to the 2015 revised IPND criteria in clinical scenarios where serum AQP4-IgG is not detectable. This is especially problematic given that some core clinical characteristics, particularly those that are suggestive of NMOSD, may eventually develop into definite NMOSD despite negative AQP4-IgG serology, such as area postrema syndrome (APS).

Based on the term "limited form of NMO,"[3] the "limited form of NMOSD" (LF-NMOSD) was introduced in this study to define patients with inaugural forms of NMOSD, including isolated APS, recurrent isolated optic neuritis (ON) with severe residual impairment of visual acuity (VA) (lower than 20/200), isolated longitudinally extensive transverse myelitis (LETM), simultaneous short-segment transverse myelitis (SSTM), and one of the other core clinical characteristics. We hypothesized that definite NMOSD can manifest after LF-NMOSD has been present for years. Given the higher risk of relapse for NMOSD regardless of AQP4-IgG serology, a therapeutic strategy for attack prevention needs to be proposed for patients with LF-NMOSD. We therefore conducted this prospective cohort study to determine the clinical course, longitudinal AQP4-IgG serostatus, therapeutic response, and outcome of patients at the onset of LF-NMOSD.

METHODS

Patient cohort, and inclusion and exclusion criteria

This study enrolled 24 patients with LF-NMOSD as defined above from November 2012 to June 2021 in the Multiple Sclerosis Center of Third Affiliated Hospital of Sun Yat-sen University. All patients were initially seronegative for AQP4-IgG as determined by a cell-based assay (CBA) prior to referral to our center. The exclusion criteria were as follows: 1) uncertain AQP4-IgG serostatus or presumed false-negative AQP4-IgG serological results due to inappropriate assay methods; 2) positive status of autoantibodies associated with paraneoplastic syndrome or autoimmune encephalitis; or 3) MRI highly indicative of other etiologies, including tumors, genetic inheritance, infection, metabolic/toxic disorders, vasculitis, and vascular malformation. The study was approved by the ethics committee of Third Affiliated Hospital of Sun Yat-sen University (Guangzhou, China; approval no. [2019]02-362-01). Written informed consent was obtained from all participants.

Follow-up and clinical onset phenotypes

All patients had been prospectively visited, and their demographics, attack-related clinical symptoms, Expanded Disability Status Scale (EDSS), modified Rankin Scale (mRS), laboratory test results, AQP4-IgG and myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG) serologies, MRI characteristics, therapeutic management, and outcome were all collected during regular follow-ups in outpatient clinics. An acute episode was defined as a neurological deficit persisting for at least 24 hours that occurred at least 30 days after the last clinical attack.[5] Acute diencephalic syndrome (ADS) was defined as symptomatic narcolepsy associated with lesions in the hypothalamus.[4] APS was defined as intractable nausea, vomiting, or hiccups persisting for more than 48 hours in association with a lesion in the dorsal medulla.[6] MRI lesion patterns suggestive of NMOSD were determined by two experienced neurologists.

Laboratory tests

Lumbar puncture was conducted in 23 of the included patients during an acute episode; the remaining patient declined the procedure. Pleocytosis was defined as a white blood cell count in cerebrospinal fluid (CSF) of >5 cells/μL. The AQP4-IgG and MOG-IgG serologies were assessed in each patient at the time of referral to our center, and repeated if necessary. The AQP4-IgG serology was assessed by CBA using live transfected cells expressing human AQP4, which is recommended as the optimal method.[7] The MOG-IgG serology was assessed by CBA using live cells transfected with full-length human MOG as reported previously.[8] To reduce the risk of false-negative results during immunosuppressive treatment, such as impulsive intravenous methylprednisolone (IVMP), AQP4-IgG serological tests were all performed as soon as possible during an acute clinical attack. AQP4-IgG serological tests were performed before initiating apheresis in one patient receiving plasma exchange (PE) and immunoadsorption due to two severe clinical relapses.

Therapeutic management and outcome

IVMP combined with or without intravenous immunoglobulin (IVIg) was adopted as the first-line treatment during the acute phase. PE or immunoadsorption was suggested in patients with severe residual disability after IVMP. During the remission phase, immunosuppressants were recommended for attack prevention according to the Chinese NMOSD therapeutic consensus. The pretreatment and posttreatment annualized relapse rates (ARRs) were calculated to evaluate the efficacy of immunosuppressants. The ARRs were assessed only if both pretreatment and posttreatment duration were no less than 6 months. The EDSS and mRS were used to assess the residual functional disability in the final interview.

Statistical analysis

Quantitative variables conforming to a normal distribution are described using mean±standard-deviation values, while other quantitative variables are described using median and interquartile-range (IQR) values. The ARR was defined as the total number of relapses divided by the total observation period in years. The pretreatment and posttreatment ARRs were compared using the Wilcoxon test. Fisher's exact test was conducted to analyze differences in lesion patterns between patients with isolated/mixed APS onset and those with non-APS onset. Kaplan-Meier analysis and survival curves were used to evaluate the risk of the first relapse and conversion to AQP4-IgG seropositivity. Cox proportional-hazards regression analysis was used to identify risk factors associated with conversion to AQP4-IgG seropositivity. Statistical analyses were conducted using SPSS software (version 23, IBM Corp., Armonk, NY, USA) and Prism software (version 8.0, GraphPad, La Jolla, CA, USA). A two-tailed probability value of $p<0.05$ was considered statistically significant.

RESULTS

Demographics and final diagnostic categories

Table 1 presents the demographics and clinical profile of the patients with LF-NMOSD. All 24 included patients were Asian adults, and their female-to-male ratio was 5:1 and their onset age was 38.1±12.0 years. The female preponderance in this cohort was less prominent than that reported in AQP4-IgG-seropositive NMOSD (9:1).[9] The median interval from disease onset to first referral to our center was 12.0 months (IQR=4.3–176.0 months). The median disease course was 73.5 months (IQR=44.3–117.0 months), and the follow-up lasted 54.2±23.8 months. At the end of the last follow-up, the final diagnosis among the 24 included patients was AQP4-IgG-seronegative NMOSD in 16 (66.7%), AQP4-IgG-seropositive NMOSD in 7 (29.2%), and MS in 1 (4.2%).

Serological status of AQP4-IgG and laboratory results

The AQP4-IgG serological tests assessed by CBA in all included patients were negative prior to the first referral to our center. The median interval from onset to the first detection of AQP4-IgG was 6.5 months (IQR=1.0–47.3 months). The median detection interval was 15.0 months (IQR=1.8–27.0 months) in 62 AQP4-IgG serological assays. At the end of the last visit, 7 of the 24 patients (29.2%) experienced conversion to AQP4-IgG seropositivity. Five patients were tested two times and two patients were tested three times during an interval of 37.9±21.9 months from the first onset to conversion to AQP4-IgG seropositivity.

Table 1. Clinical profile of the cohort with the limited form of neuromyelitis optica spectrum disorders at the first onset

Clinical characteristic	Value
Age at disease onset, years	38.1±12.0
Sex ratio, female:male	5:1
Disease duration, months	73.5 (44.3–117.0)
Follow-up, months	54.2±23.8
Clinical onset phenotypes	
Isolated/mixed APS	9/24
Isolated ON with severe VA impairment	8/24
SSTM + ON/ADS	4/24
LETM + ON	2/24
Isolated LETM	1/24
Clinical relapse phenotypes	
AM	27/60
Isolated ON	18/60
Simultaneous ON + AM	4/60
Isolated APS	4/60
Others	7/60
Number of relapses	2.46±1.25
ARR	0.37 (0.13–0.63)
CSF features*	
Pleocytosis (WBC count >5 cells/mL)	5/23
CSF protein >0.4 g/L	7/23
Positive for OCBs	1/23
Serological status of AQP4-IgG	
Interval from onset to first AQP4-IgG detection, months	6.5 (1.0–47.3)
Interval of serum AQP4-IgG detection, months	15.0 (1.8–27.0)
Patients with AQP4-IgG seropositivity	7/24
Interval from onset to first seropositive conversion, months	37.9±21.9
Transient MOG-IgG seropositivity	1/24
Positive for ANA	6/24
Complicated with Sjögren's syndrome	1/24
Final diagnosis	
AQP4-IgG-seronegative NMOSD	16/24
AQP4-IgG-seropositive NMOSD	7/24
Multiple sclerosis	1/24
Pretreatment EDSS†	2.8 (2.0–3.5)
Posttreatment EDSS†	1.5 (1.0–2.0)

Data are mean±standard-deviation, *n*, or median (interquartile range) values.
*One patient declined lumbar puncture examination; †Pretreatment and posttreatment EDSS indicate EDSS assessments performed before and after long-term immunosuppressive therapy (>6 months).
ADS, acute diencephalic syndrome; AM, acute myelitis; ANA, antinuclear antibody; APS, area postrema syndrome; AQP4-IgG, aquaporin-4 immunoglobulin G; ARR, annualized relapse rate; CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; LETM, longitudinally extensive transverse myelitis; MOG-IgG, myelin oligodendrocyte glycoprotein immunoglobulin G; OCBs, oligoclonal bands; ON, optical neuritis; SSTM, short-segment transverse myelitis; VA, visual acuity; WBC, white blood cell.

The clinical course and longitudinal AQP4-IgG serostatus are demonstrated in Fig. 1. One in seven patients who experienced conversion to AQP4-IgG seropositivity also experienced transient MOG-IgG seropositivity, but they were diagnosed with seropositive NMOSD based on the neuroimaging characteristics in MRI. The MOG-IgG serology was retested in this patient 20 months later, and the result was negative. Positive oligoclonal bands (OCBs) in CSF were found in only one patient who finally met the 2017 MacDonald MS diagnostic criteria[10] after more than five years of follow-up. The MOG-IgG serology was negative for the remaining 16 patients diagnosed with AQP4-IgG-seronegative NMOSD. Pleocytosis was found in five patients, and slight elevation of CSF proteins was found in seven patients. Six patients were positive for antinuclear antibody (ANA). Two of these six patients showed an ANA pattern consistent with Sjögren's syndrome: the one with anti-SSA/Ro antibody was asymptomatic, and the other with both anti-SSA/Ro and anti-SSB/La antibodies was finally diagnosed with Sjögren's syndrome based on dryness symptoms and an inner lip gland biopsy revealing the focal infiltration of lymphocytes around the salivary gland.

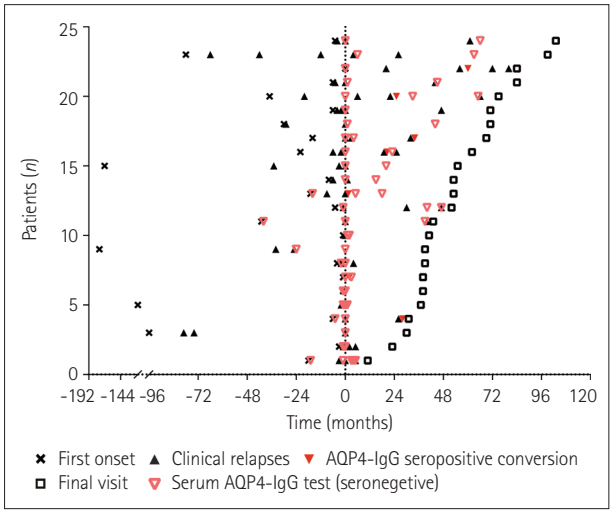

Fig. 1. Clinical course and longitudinal aquaporin-4 immunoglobulin G (AQP4-IgG) serostatus in patients with the limited form of neuromyelitis optica spectrum disorders and negative AQP4-IgG serology at disease onset.

A Cox proportional-hazards regression model was utilized to explore the risk factors associated with AQP4-IgG serological conversion (Table 2). The multivariate analysis indicated that isolated/mixed APS onset (hazard ratio [HR]=28.006, 95% confidence interval [CI]=1.248–628.399, p=0.036) and multiple AQP4-IgG tests (HR=16.364, 95% CI=1.879–142.488, p=0.011) were independent risk factors for conversion to AQP4-IgG seropositivity after adjusting for age at disease onset, female sex, and a time to first relapse of ≤1 year.

Characteristics of clinical course

The final diagnostic categories of this cohort are summarized in Fig. 2A. Based on the classifications of onset phenotypes, isolated/mixed APS (n=9) was the most common onset phenotype, followed by isolated ON with severe VA impairment (n=8), SSTM+ON/ADS (n=4), LETM+ON (n=2) and isolated LETM (n=1) (Fig. 2B). Isolated/mixed APS onset phenotypes accounted for 23.5% and 71.4% of the AQP4-IgG-seronegative and -seropositive NMOSD patients, respectively (p=0.061) (Fig. 2C). All patients experienced a multiphasic disease course, with a median ARR of 0.37 (IQR=0.13–0.61) and 2.46±1.25 relapses. Among the 60 relapses in this cohort, acute myelitis (AM) (n=27, 45.0%) was the most frequent relapse phenotype, followed by isolated ON with severe VA impairment (n=180, 30.0%), simultaneous ON+AM (n=4, 6.7%), APS (n=4, 6.7%), and others (n=7, 11.7%). The classification of relapse phenotypes did not differ significantly between AQP4-IgG-seronegative and -seropositive NMOSD (p=0.197) (Fig. 2D).

As presented above, isolated/mixed APS followed by isolated ON with severe VA impairment was the predominant onset phenotype in this cohort. Survival analysis was conducted to determine whether the onset phenotype predicted the risk of first relapse as well as the risk of conversion to AQP4-IgG seropositivity. As shown in Fig. 3A, the risk of first relapse did not differ significantly between patients with isolated/mixed APS onset and those with non-APS onset (HR=0.936, 95% CI=0.396–2.216, p=0.874), nor between those with isolated/mixed ON onset and those with non-ON onset (HR=0.748, 95% CI=0.317–1.767, p=0.467) (Fig. 3B). Consistent

Table 2. Findings of Cox proportional-hazards regression for factors associated with conversion to AQP4-IgG seropositivity

	β	Wald χ^2	HR	95% CI	p
Age at disease onset	-0.059	0.676	0.943	0.820–1.085	0.411
Female sex	-1.222	0.276	0.295	0.003–28.082	0.599
Isolated/mixed APS onset	3.332	4.408	28.006	1.248–628.399	0.036*
Time to first relapse ≤1 year	-0.461	0.152	0.631	0.062–6.413	0.697
Multiple AQP4-IgG tests	2.795	6.407	16.364	1.879–142.488	0.011*

*Asterisk indicates a significant effect.
APS, area postrema syndrome; AQP4-IgG, aquaporin-4 immunoglobulin G; CI, confidence interval; HR, hazard ratio.

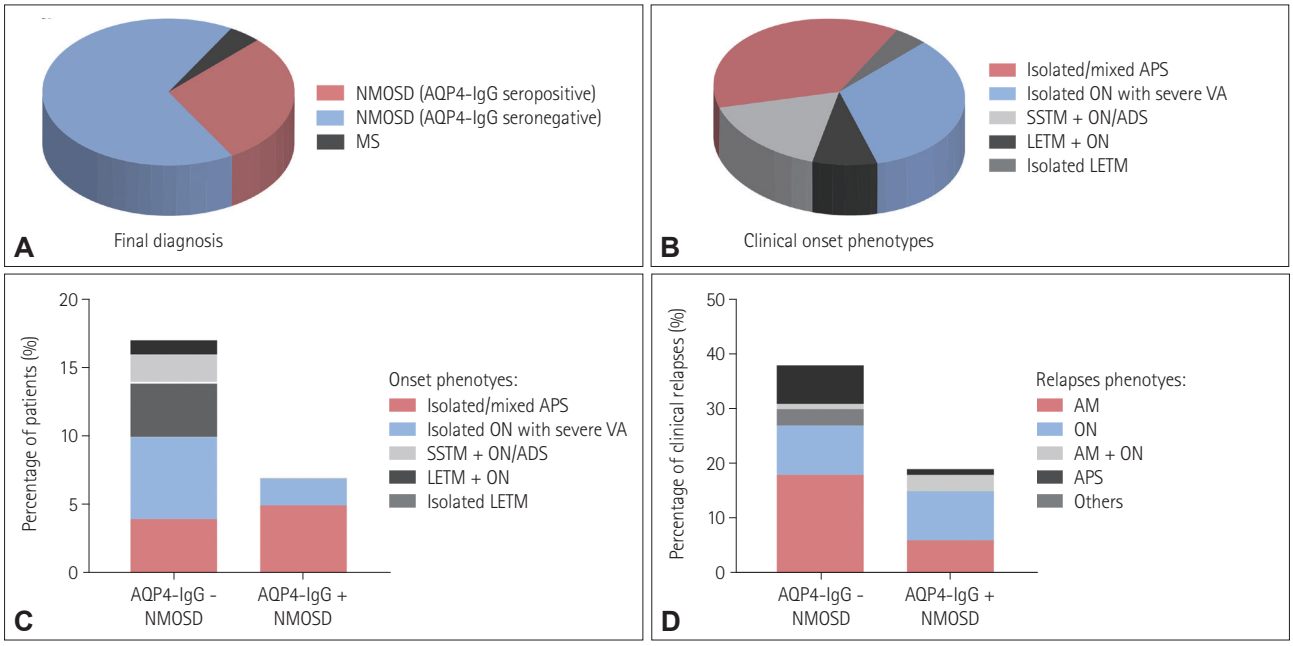

Fig. 2. A: Categorization of diagnoses at the final visit. B: Proportions of clinical onset phenotypes. C: Isolated/mixed APS accounted for 23.5% and 71.4% of onset phenotypes in AQP4-IgG-seronegative and -seropositive NMOSD, respectively (p=0.0606). D: AM and ON were the primary relapse phenotypes in 60 clinical relapses. The relapse phenotypes did not differ significantly between AQP4-IgG-seronegative and -seropositive NMOSD (p=0.1970). ADS, acute diencephalic syndrome; AM, acute myelitis; APS, area postrema syndrome; AQP4-IgG, aquaporin-4 immunoglobulin G; LETM, longitudinally extensive transverse myelitis; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders; ON, optical neuritis; SSTM, short-segment transverse myelitis.

with the Cox proportional-hazards regression model for predicting AQP4-IgG serological conversion, as described above, patients with isolated/mixed APS onset showed a predilection for conversion to AQP4-IgG seropositivity, although the difference was not significant, which might have been due to the smallness of the sample in our cohort (HR=4.053, 95% CI=0.882−18.620, p=0.069) (Fig. 3C). However, the risk of conversion to AQP4-IgG seropositivity did not differ significantly between patients with isolated/mixed ON onset and those with non-ON onset (HR=0.408, 95% CI=0.086−1.924, p=0.220) (Fig. 3D).

Longitudinal MRI

Fig. 4 presents representative neuroimaging results for the longitudinal radiological development of typical cases in the present cohort. Longitudinal neuroimaging revealed the transformation from LF-NMOSD at disease onset to definite NMOSD. The findings of neuroimaging comparisons between patients with isolated/mixed APS onset phenotype and those with non-APS onset are summarized in Supplementary Table 1 (in the online-only Data Supplement). Briefly, the lesion pattern in the supratentorial brain and spinal cord did not differ significantly between the two groups (see each p value in Supplementary Table 1 in the online-only Data Supplement). Optic nerve involvement, including increased signal on T2-weighted imaging or enhancement on T1-weighted imaging with gadolinium contrast throughout the optic nerve, was more prevalent in patients with non-APS onset than in those with isolated/mixed APS onset (p=0.0215).

Treatment and prognosis

IVMP was the most prevalent treatment in the acute phase in 84 clinical episodes, including 60 relapses, while the combination treatment of IVMP and IVIg was used in 18 clinical episodes of 13 patients. PE and immunoadsorption were introduced in one patient who experienced two episodes of recurrent LETM within 6 months. During the remission phase, 17 patients were prescribed azathioprine (2−3 mg/kg daily) or mycophenolate mofetil (1.0−1.5 g daily), and only 11 patients remained relapse-free during a follow-up of 35.1±23.7 months. Among the patients treated with other immunosuppressants, one taking rituximab (700 mg biweekly for every 6 months), one taking methotrexate (10 mg weekly), one taking tacrolimus (0.5 mg twice daily), and one taking intravenous cyclophosphamide (1.0 g monthly for up to 6 months) achieved sustained remission during a follow-up of 38.3±7.0 months. Two patients treated with a daily dose of 8-mg methylprednisolone or 10-mg prednisone remained relapse-free for more than 48 months. Seven patients switched immunosuppressants, which was due to primary treatment failure in four (three for azathioprine and one for mycophenolate mofetil) and to azathioprine-associated side effects in three. The clini-

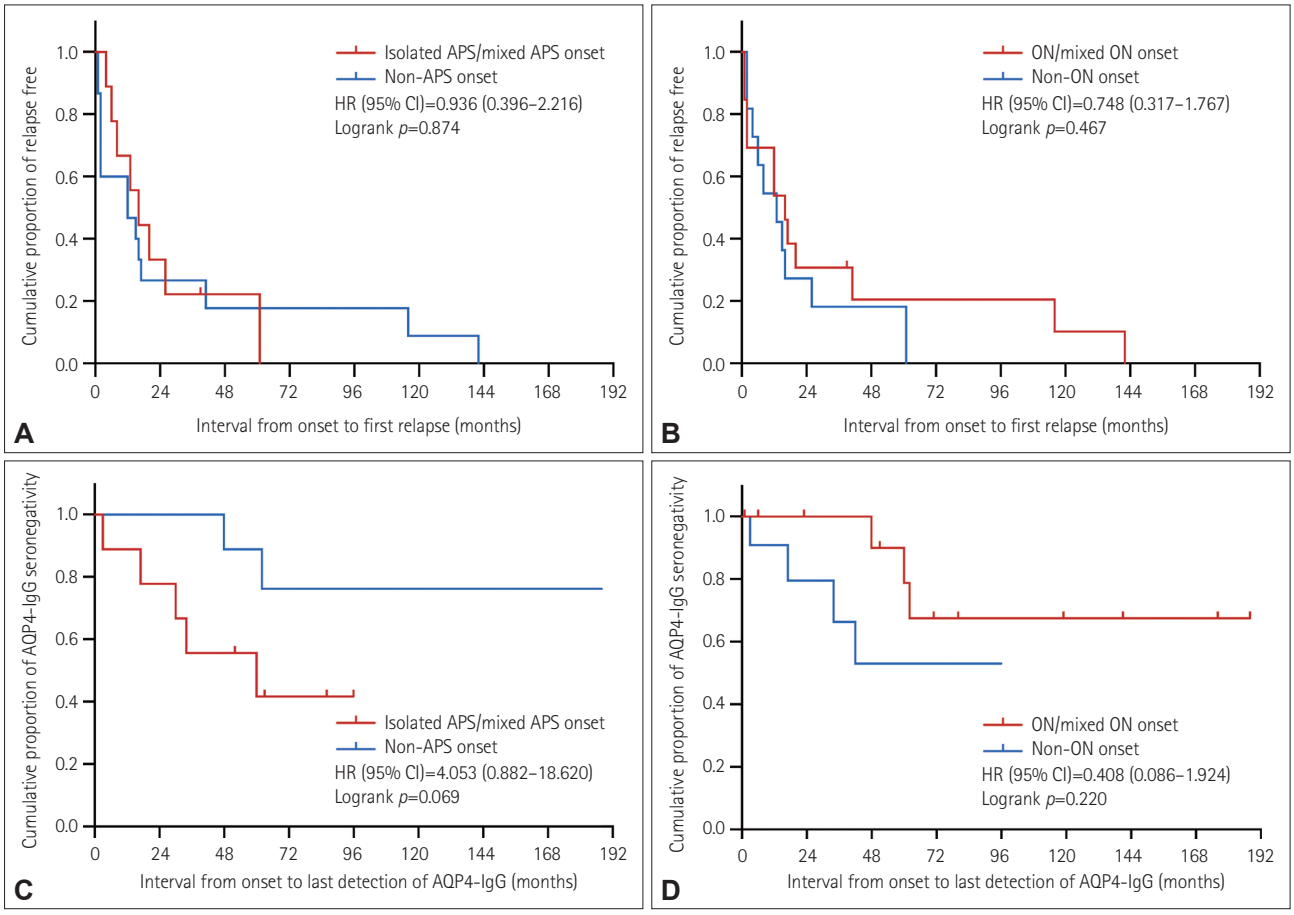

Fig. 3. Results of survival analysis for determining the risk of first relapse and conversion to AQP4-IgG seropositivity. A: The risk of first recurrence did not differ significantly between patients with isolated/mixed APS onset and those with non-APS onset (HR=0.936, 95% CI=0.396–2.216, *p*=0.874). B: Patients with isolated/mixed ON onset and those with non-ON onset were also included (HR=0.748, 95% CI=0.317–1.767, *p*=0.467). C: Patients with isolated/mixed APS onset showed a nonsignificant predilection for developing conversion to AQP4-IgG seropositivity compared with those with non-APS onset (HR=4.053, 95% CI=0.882–18.620, *p*=0.069). D: The risk of developing AQP4-IgG serological conversion did not differ significantly between patients with isolated/mixed ON onset and those with non-ON onset (HR=0.408, 95% CI=0.086–1.924, *p*=0.220). APS, area postrema syndrome; AQP4-IgG, aquaporin-4 immunoglobulin G; CI, confidence interval; HR, hazard ratio; ON, optical neuritis.

cal episodes before and after the initiation of immunosuppressants are illustrated in Fig. 5. The median pretreatment and posttreatment EDSS scores were 2.8 and 1.5, respectively, favoring the immunosuppressive therapy in patients with LF-NMOSD at disease onset. No patient became wheelchair-dependent (mRS >3 or EDSS >6) despite residual disability, including impaired VA, motor defects, and sphincteric disturbance.

DISCUSSION

This prospective cohort study investigated the clinical course, therapeutic management, and outcomes of patients with LF-NMOSD at disease onset. All but one of the patients were diagnosed with NMOSD, suggesting a high risk of developing to definite NMOSD in patients with LF-NMOSD at disease onset. Few studies have longitudinally investigated the AQP4-IgG serostatus in NMOSD, and the proportion of patients with inaugural AQP4-IgG-negative serology experience conversion to AQP4-IgG seropositivity remains unknown. In the present cohort, 29.2% of patients with initial negative AQP4-IgG serology identified by CBA experienced conversion to AQP4-IgG seropositivity. The mean interval from the first onset to conversion to AQP4-IgG seropositivity exceeded 36 months. Furthermore, multiple tests increased the probability of the conversion to AQP4-IgG seropositivity. Although it remains controversial whether AQP4-IgG titers are correlated with clinical disease activity,[11-13] AQP4-IgG seropositivity is predictive of a higher risk of relapse[14] and the progression to NMOSD.[11,15,16] It is therefore of therapeutic and prognostic significance to monitor AQP4-IgG serology so that a proactive preventive strategy can be applied to patients with LF-NMOSD at disease onset. Moreover, there is little agreement about the optimal test interval of AQP4-IgG assays for patients with a

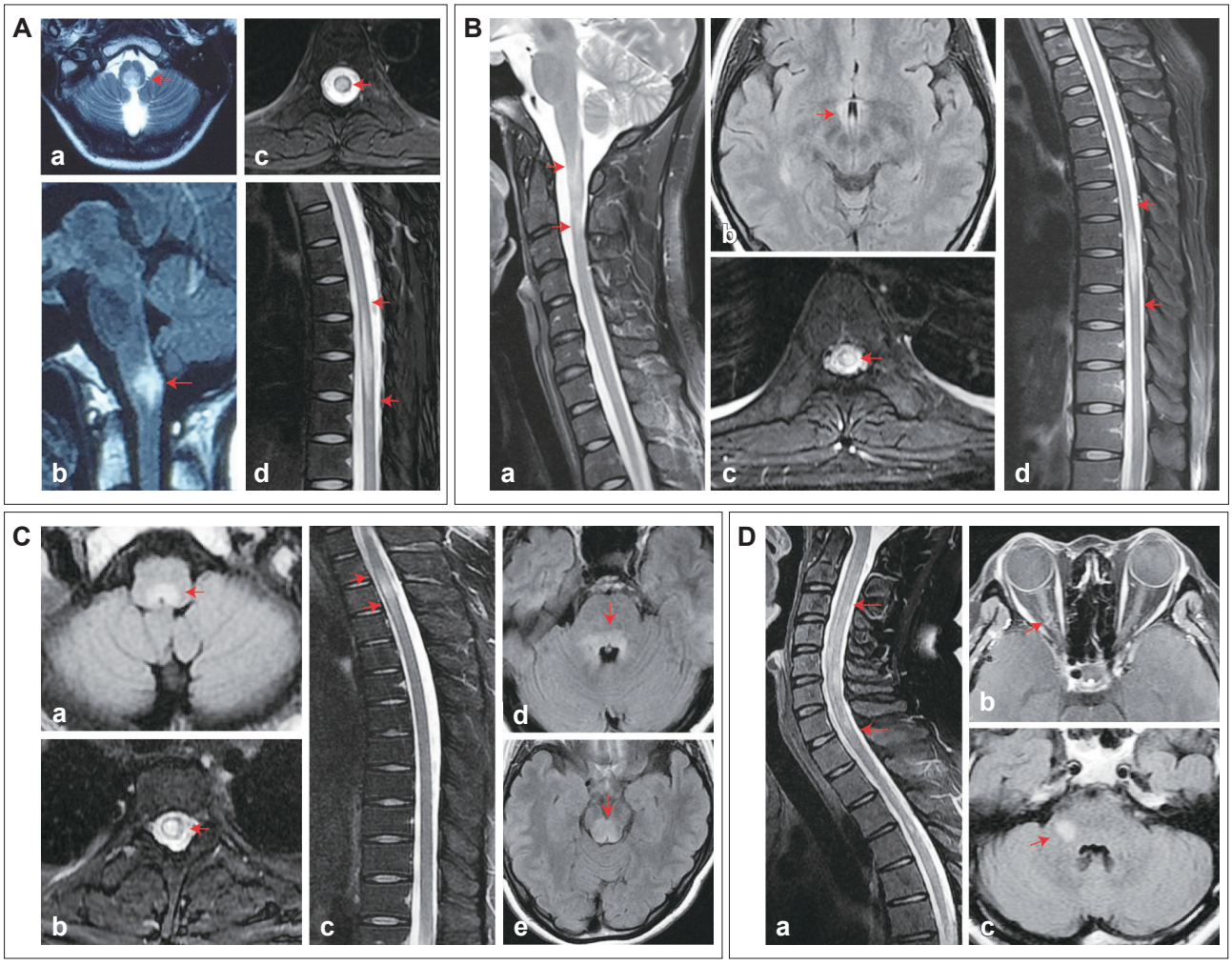

Fig. 4. Representative MRI findings in this cohort. A: A 26-year-old female patient presented with intractable nausea, vomiting, and hiccups with a lesion in the area postrema of the dorsal medulla (a: axial view; b: sagittal view) in June 2018, and suffered from LETM (c: axial view; d: sagittal view) in March 2021. B: A 29-year female patient who was admitted to the hospital for simultaneous SSTM (a) and symptomatic narcolepsy associated with a lesion in the diencephalon (b) in January 2019 experienced LETM (c: axial view; d: sagittal view) in December 2020. C: Another 29-year-old female patient suffered from simultaneous area postrema syndrome (a) and SSTM (b: axial view; c: sagittal view) in September 2016, followed by an attack of acute brainstem syndrome with periependymal lesions around the pons (d) and dorsal midbrain (e) in January 2017. D: A 36-year-old male patient with suspected opticospinal MS based on simultaneous LETM (a) and optic neuritis (b) in November 2012, was finally diagnosed with MS after more than 5 years of follow-up. He experienced left facial numbness associated with a cerebellar peduncle lesion supportive of MS (c) in December 2017. LETM, longitudinally extensive transverse myelitis; MS, multiple sclerosis; SSTM, short-segment transverse myelitis.

strong suspicion of NMOSD. Clinical observations suggest that a retesting interval of 3–6 months is desirable in patients with negative AQP4-IgG serology.[7] It is worth mentioning that the risk of false serological negativity may increase during remission when being treated with immunosuppressants or B-cell-depleting agents.[12,13,17] In our cohort, seven patients experienced conversion to AQP4-IgG seropositivity: two within 3 months after the last relapse and five during acute attacks. We therefore strongly recommend retesting AQP4-IgG serology during an acute episode or within 3 months after the last attack.

The correspondence of the lesion patterns with the AQP4-enriched regions, including the area postrema, hypothalamus, and periependymal regions surrounding the ventricle,[18] strongly supports the diagnosis of NMOSD in clinical scenarios without detectable serum AQP4-IgG. In particular, APS has been recognized as one of the six core clinical characteristics of NMOSD.[4] The reported frequencies of isolated and mixed APS onset in AQP4-IgG-seropositive NMOSD have been 7.1%–10.3% and 8.2%–15.9%, respectively.[6] For our cohort, the frequency of isolated/mixed APS onset was 45.8%, which is remarkably higher than that reported in AQP4-IgG-seropositive NMOSD. Moreover, patients with isolated/mixed APS onset showed a predilection for conversion to AQP4-IgG se-

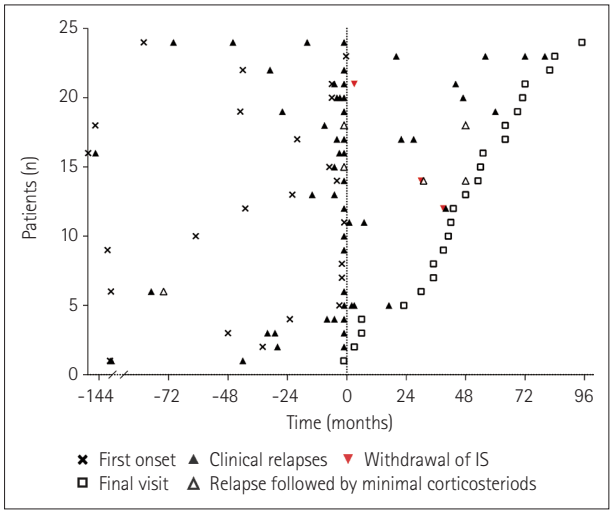

Fig. 5. Clinical episodes of the patients before and after initiation of immunosuppressant (IS) treatment.

ropositivity. Consistent with studies favoring the specificity of APS in NMOSD,[6,19,20] all of our patients with isolated/mixed APS eventually developed definite NMOSD regardless of the AQP4-IgG serostatus. Isolated/mixed APS onset usually preceded ON or AM in our cohort, making APS a warning sign for developing definite NMOSD. It is therefore necessary to attach more clinical significance to long-term follow-up in patients with isolated/mixed APS onset. In contrast, there was no APS predominance in recurrent attacks in the present cohort, suggesting that APS responds favorably to immunotherapeutic maintenance.[6]

Coincidentally, AQP4-IgG-seronegative NMOSD with isolated APS onset was recently found in a retrospective study, but this hypothesis has rarely been discussed.[21] Assuming that false-negative AQP4-IgG results due to inappropriate methodology or immunosuppressive treatment can be excluded, the following explanations may account for the negative AQP4-IgG serology in patients with APS onset. Firstly, patients with APS onset (in particular isolated APS) usually present to a department of gastroenterology or psychiatry instead of a department of neurology, which can lead to substantial delays in diagnosis as well as in the performing of AQP4-IgG serological tests. Clinical data regarding the interval from APS onset to the occurrence of detectable serum AQP4-IgG are not yet available. Secondly, unlike the pathological severity of transverse myelitis and ON, the pathology of area postrema lesions in NMOSD is mainly characterized by the loss of AQP4 immunoreactivity and inflammation, without the presence of demyelination or necrosis.[22] Thirdly, isolated APS seems self-limited even without immunotherapy in some individuals. Together these observations indicate that whether the individual heterogeneity of activated inflammation and humoral immunity influences AQP4-IgG serology remains elusive.

It is significant but challenging to distinguish LF-NMOSD from opticospinal MS in clinical practice. Demographically, the local MS prevalence and OCB status in the CSF may influence diagnostic preferences.[23] In China, expert clinicians usually give more consideration to diagnosing AQP4-IgG-seronegative NMOSD than MS, since the prevalence of MS is markedly lower in Asians than in the White population (5–50/100,000 and 100–200/100,000, respectively).[24] Radiologically, LETM has been considered a distinctive discriminator between NMOSD and opticospinal MS.[23] However, myelitis involving spinal lesions shorter than three vertebral segments cannot absolutely preclude AQP4-IgG-seronegative NMOSD.[25,26] In the present cohort, all four patients with simultaneous SSTM+ON eventually developed NMOSD. Moreover, SSTM is a common relapse phenotype in patients with LF-NMOSD. This strengthens the importance of clinical and radiological follow-up in patients with LF-NMOSD, even though the additional neuroimaging requirements described in the 2015 revised IPND criteria might not be satisfied at the disease onset.

Given that no relevant previous studies have specified the treatment of inaugural LF-NMOSD, we developed therapeutic strategies mainly based on the international management guidelines of NMOSD.[27-29] IVMP followed by oral corticosteroid tapering was the most-prevalent first-line treatment during acute attacks in this cohort. Impaired VA, sphincteric dysfunction, and tonic spasm were the primary complaints during remission visits. Notably, one patient without detectable serum AQP4-IgG received PE and immunoadsorption during two relapses of LETM after failing to respond to IVMP, and exhibited a favorable treatment response. Some published studies have demonstrated the superiority of apheresis (immunoadsorption or PE) over IVMP[5,30] in NMOSD. Apheresis may be reasonable for patients with a severe attack regardless of AQP4-IgG serology if there are no known contradictions. Further studies are necessary to validate the efficacy of apheresis therapy in patients without detectable serum AQP4-IgG. During the remission phase, immunosuppressive therapy reduced the clinical relapses and accumulation of functional disability as assessed by the pretreatment and posttreatment ARRs and EDSS. Therefore, immunosuppressive therapy is reasonable and safe in patients with LF-NMOSD at disease onset.

In conclusion, this study strengthens the clinical importance of long-term follow-up and immunotherapy management in patients with LF-NMOSD at disease onset. In particular, an isolated/mixed APS onset shows a predilection for conversion to AQP4-IgG seropositivity and is predictive of a high risk of developing definite NMOSD. Future large-cohort studies are warranted to investigate the clinical course and individualized immunotherapeutic management of patients

with LF-NMOSD at disease onset.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.4.453.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due to the privacy protection for patients but are available from the corresponding author on reasonable request.

ORCID iDs

Xiaodong Chen	https://orcid.org/0000-0002-9094-4691
Jing Zhou	https://orcid.org/0000-0002-2018-1924
Rui Li	https://orcid.org/0000-0002-1932-3737
Bingjun Zhang	https://orcid.org/0000-0002-9641-2485
Yuge Wang	https://orcid.org/0000-0003-3005-6163
Xiaonan Zhong	https://orcid.org/0000-0001-9853-012X
Yaqing Shu	https://orcid.org/0000-0003-2768-1654
Yanyu Chang	https://orcid.org/0000-0002-3226-1008
Wei Qiu	https://orcid.org/0000-0002-0880-958X

Author Contributions

Conceptualization: Wei Qiu. Data Curation: Xiaodong Chen, Jing Zhou. Funding acquisition: Wei Qiu. Investigation: Xiaodong Chen, Jing Zhou, Rui Li, Xiaonan Zhong, Yanyu Chang, Yaqing Shu, Yuge Wang. Methodology: Xiaodong Chen, Yuge Wang, Yaqing Shu, Bingjun Zhang. Supervision: Wei Qiu. Writing—original draft: Xiaodong Chen. Writing—review & editing: Wei Qiu.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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