Aging, immunosenescense, and very late-onset neuromyelitis optica spectrum disorders

Keiichi Nakahara
Kumamoto Daigaku
Shunya Nakane (nakaneshunya@gmail.com)
Kumamoto University Hospital https://orcid.org/0000-0003-1958-095X
Yukio Ando
Kumamoto Daigaku

Research

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Abstract

Objective: To clarify the clinical features of very late-onset neuromyelitis optica spectrum disorders NMOSD (VLO-NMOSD).

Methods: According to the age at onset, we classified patients with NMOSD into three subgroups of early-onset NMOSD (EO-NMOSD), late-onset NMOSD (LO-NMOSD), and VLO-NMOSD. We evaluated the clinical characteristics, MRI findings, laboratory data, and immunotherapies among the groups.

Results: Overall, eight males and 36 females with a median age at onset of 43.00 years (interquartile range, 29.00–54.75) and median duration of disease of 6.00 months (interquartile range, 3.00–11.75) were included. This included 7 (16%) patients with VLO-NMOSD, 11 (25%) with LO-NMOSD, and 26 (59%) with EO-NMOSD. Patients with EO-NMOSD had significantly longer disease duration than those did with VLO-NMOSD and LO-NMOSD (p=0.015). Optic nerve lesions on MRI and optic neuritis were significantly less frequent in patients with VLO-NMOSD than in those with LO-NMOSD and EO-NMOSD (p=0.013 and p=0.046, respectively), whereas the length of the spinal lesion was significantly longer in those with VLO-NMOSD in comparison with those with LO-NMOSD and EO-NMOSD (p=0.038).

Conclusions: Spinal cord lesion in patients with VLO-NMOSD was significantly longer despite short disease duration, and optic neuritis was significantly less frequent in them.

Background

Aging is defined as “physiologically progressive, generalized degeneration and decay of somatic tissues and immune system (immunosenescence) with increasing probability of death” [1]. Immunosenescence is best known in T-cell subsets in the form of cellular and molecular alterations and thymic atrophy, which result in reduced function of T- and B-cells [2-4]. Immunosenescence is prone to autoimmune responses and the incidences of several autoimmune diseases are higher, or are preferentially encountered, in the elderly [5, 6]. We previously reported on the incidence of elderly-onset myasthenia gravis (MG) in Japan, and discussed the relationship between the clinical features and immunological background [7].

Neuromyelitis optica spectrum disorders (NMOSD) is a severe autoimmune demyelinating disorder that primarily affects the optic nerve and spinal cord [8]. Various immune dysregulations have been identified in patients with NMOSD. These dysregulations result in autoantibodies (Abs) and chronic immune-mediated inflammation in central nervous system (CNS) [9-13]. Anti-aquaporin 4 (AQP4) Abs are highly specific for NMOSD [9, 10, 12, 14] The usual age of onset in NMO is the 30s or 40s [15]; however, NMOSD in the elderly has recently been reported as not uncommon [16, 17]. Older patients with NMOSD often present with insidious onset of symptoms and aggressive progression [18-23], which inspired articles on late-onset NMOSD (LO-NMOSD) [21, 24, 25]. Although few papers have reported anecdotally on very late-onset (VLO)-NMOSD [18, 19, 23-26], case series with a focus on VLO-NMOSD are rare. Therefore, the aim of this retrospective study was to identify the clinical features of VLO-NMOSD as compared to early and late onset groups.

Results

Clinical features and laboratory findings of patients with NMOSD

Table 1 summarizes the results of the clinical features in each group. Overall, the patients included eight males and 36 females with a median age of onset of 43.00 years (interquartile range, 29.00–54.75) and median duration of disease of 6.00 months (interquartile range, 3.00–11.75). Of the 44 patients, 7 (16%) were identified to have VLO-NMOSD, 11 (25%) as LO-NMOSD, and 26 (59%) as early-onset (EO)-NMOSD. Patients with EO-NMOSD had significantly longer disease duration than did those with VLO-NMOSD and LO-NMOSD (p=0.015). Optic neuritis in patients with VLO-NMOSD was significantly less frequent than in those with LO-NMOSD and EO-NMOSD (p=0.029). The interval between episodes and time between the first symptom and diagnosis of NMOSD were significantly longer in patients with EO-NMOSD when compared with those with VLO-NMOSD and LO-NMOSD (p=0.046). No significant differences were observed in the Charlson comorbidity index, onset symptoms, the expanded disability status scale (EDSS) score, Nurick scale score, immunotherapies, and laboratory findings (Tables 1 and 2).

Brain and spinal cord MRI findings

Optic nerve lesions were observed significantly less frequently in patients with VLO-NMOSD (p=0.013, Table 3), whereas the length of the spinal lesion was significantly longer in these patients (p=0.038, Table 3). Figure 1 depicts the typical spinal MRIs in patients with VLO-NMOSD, LO-NMOSD, and EO-NMOSD.

Illustrative cases of VLO-NMOSD

- **Case 1**: An 81-year-old woman experienced numbness in her legs and severe quadriplegia with urinary retention for 5 days. Spinal MRI demonstrated a long cord lesion extending from C2 to T5. Serum test for AQP4 Abs was positive. She received intravenous methylprednisolone (IVMP) at a dose of 1 g/day for 3 days without signs of improvement. Two weeks after the initial IVMP, she experienced rapidly progressive visual loss in both eyes, which culminated in complete blindness within 5 days. She received a second course of IVMP for 5 days with oral tapering of steroids. Consequently, her visual deficit improved slightly. Finally, 10 days after the second cycle of IVMP, she developed excessive bleeding from a rectal ulcer and shock. Currently, she is 83 years old and had been bedridden for approximately 2 years.
- **Case 2**: A 77-year-old man experienced hiccups and severe paraplegia for 2 weeks. Spinal MRI demonstrated a very long cord lesion extending from C7 to the conus. Serum test for AQP4 Abs was positive. Shortly after, he experienced rapidly progressive quadriplegia, dyspnea, and severe visual loss in both eyes. On repeat spinal MRI, the spinal cord lesion now extended to C2. He used an artificial respirator and underwent three courses of IVMP for 5 days each over one month. Prednisolone (PSL) was orally administered because the patient needed continuous immunosuppression therapy to prevent progression of the disease. Subsequently, the patient underwent eight courses of plasma exchange of 2000 mL each and intravenous immunoglobulin

(400 mg/kg body weight/day) for 5 days without signs of improvement. Subsequently, 3 months after disease onset, his respiratory condition worsened and he died shortly thereafter.

- **Case 3**: A 72-year-old woman experienced moderate paraplegia and dysesthesia on the right side for 2 days. Spinal MRI demonstrated spinal cord lesions extending from C7 to C4 and T2 to T4. This patient was seronegative for AQP4 Abs but her serum tests for anti-nuclear antibody (ANA), rheumatoid factor (RF), and anti- SSA and SSB Abs were positive. IVMP was administered for 3 days in combination with oral PSL, which resulted in clinical improvement. Her symptoms gradually resolved, and she eventually was able to walk with a cane.

Discussion

In the present study, the clinical features, laboratory findings, and MRI findings were investigated in patients with NMOSD, with a particular focus on the age of onset. This study is the first to our knowledge to describe the clinical characteristics of patients with VLO-NMOSD. Two important results of this study were: i) spinal cord lesions in patients with VLO-NMOSD were significantly longer within short disease duration, and ii) optic neuritis was significantly less frequent in VLO-NMOSD.

Recent studies have reported that patients with EO-NMOSD tended to manifest optic neuritis as the first symptom, whereas those with LO-NMOSD tended to develop myelitis first [16, 17]. Interestingly, optic neuritis is also less frequently seen in patients with late-onset multiple sclerosis than in those with early-onset (< 50 years) multiple sclerosis [31]. Therefore, there is a possibility that the optic nerves are more vulnerable in the younger population rather than an older one. In contrast, myelitis in patients with VLO-NMOSD was very aggressive according to the findings of short disease duration and intervals between episodes when compared with patients with LO-NMOSD and EO-NMOSD. Furthermore, we observed that both EDSS score and Nurick scale tended to be higher in patients with VLO-NMOSD than those in patients with LO-NMOSD and EO-NMOSD, although the differences were not significant. We believe that the symptoms and clinical course in patients with VLO-NMOSD were severe due to very long cord lesions, as we have demonstrated with illustrative cases 1 and 2. Sepulveda et al. focused on the relationship between the serostatus for Abs and disability in patients with NMOSD divided by age groups [32]. They reported that patients with LO-NMOSD (≥50 years in that study) who had AQP4 Abs had worse outcomes over a short period of follow-up than did those with EO-NMOSD who had AQP4 Abs. Our results are in agreement with their results.

Our findings suggest that the clinical characteristics of patients with VLO-NMOSD may be related to immunosenescence, which may be importance when considering the pathogenesis of autoimmune diseases [1-6, 33]. Our findings suggest that the clinical characteristics of patients with VLO-NMOSD may be related to immunosenescence. We were interested in the results of the presence or absence of other Abs in the serum and immunoglobulin G (IgG) index in CSF as indicators of immunosenescence. In their study, Sepulveda et al. reported that concomitant autoimmune diseases were frequently confirmed in patients with LO-NMOSD [32]. In this study, the seroprevalence of ANA, the average CSF protein, and the average IgG index were higher in patients with VLO-NMOSD than in those with LO-NMOSD, although the

differences were not statistically significant. Autoimmune abnormalities in the elderly are accompanied with increased production of autoantibodies such as ANA, RF, and anti-phospholipid Abs [3]. In case 3 described above, we detected ANA, RF, and anti-SSA and SSB Abs in the patient's serum, and confirmed remarkably elevated IgG index. We considered this case as the typical case of VLO-NMOSD with immunosenescence. Although autoimmunity should not be considered an obvious characteristic of the elderly [34, 35], a large proportion of the elderly may demonstrate autoantibodies, which may be related to higher exposure to exogenous factors, such as infections and medications. Although the immunopathogenesis appears to be complex, we should verify the alterations in the immune functions due to aging in patients with VLO-NMOSD [6]. The limitations of the present study include its retrospective design and the small sample size.

Conclusions

We reported the clinical characteristics of NMOSD according to age of onset. Patients with VLO-NMOSD tended to manifest severe myelitis with long cord lesions but not optic neuritis. Prospective, interventional, multi-centre studies according to the age group are necessary to confirm the relationships between the clinical features, levels of AQP4 Abs, biomarkers (including other Abs and CSF analysis), and MRI findings versus the outcomes of immunotherapies in patients with VLO-NMOSD.

Methods

Patients and study design

We reviewed the clinical records of patients diagnosed with NMOSD who were treated at the Kumamoto University Hospital between September 2010 and July 2018. The diagnosis of NMOSD was confirmed using the 2015 criteria [27]. We identified and included 44 patients in the present study. Patients were classified as follows based on the age of disease onset: ≤ 49 y: EO-NMOSD; 50–69 y: LO-NMOSD; and ≥ 70 y: VLO-NMOSD.

All patients underwent review of full medical history and neurological examinations by at least two neurologists. Comprehensive clinical and serological assessments were performed in all patients. We extensively reviewed the following clinical information: age, sex, age of onset of first symptom, disease duration, index episode, attack interval, estimation of the disability during an acute episode and at the last visit (e.g., EDSS [28], Nurick scale score [29]), and comorbidities (e.g., Charlson comorbidity index [30]). Additionally, the following laboratory data were reviewed: qualitative data of AQP4 Abs, other Abs tests, CSF analysis and immunotherapies.

MRI evaluation of the brain and spinal cord

MRI scans at the Kumamoto University Hospital were acquired with 3-T MRI systems (Achieva, Philips Healthcare, The Netherlands; MAGNETOM Trio, MAGNETOM Prisma^{fit}, Siemens, Erlangen, Germany). These images were separately interpreted by two neurologists (KN and SN) based on the reports by the

neuroradiologist. The presence or absence of MRI lesions in the cerebrum, cerebellum, brainstem, optic nerve, and spinal cord in the cervical, thoracic, and lumber sections were evaluated. The length of the spinal cord lesions was expressed in terms of the number of vertebral segments.

Statistics

In this study observational cross-sectional study, the sample size was determined by considering the number of outpatients and inpatients at the Kumamoto University Hospital during the survey period. Categorical data (Gender, Onset symptoms, Symptoms during the course, Treatment of acute disease attacks, Long-term treatment, AQP4 Abs positive, ANA positive, Lesions of brain and spinal cord MRI) were analyzed by the χ^2 test. Non-normally distributed data (Age at onset, disease duration, Charlson comorbidity index, Time from first symptom to diagnosis of NMOSD, Total number of attacks, Attack interval, Nadir EDSS score, EDSS score at last visit, Serum IgG, CSF analysis, Length of spinal lesion) were compared in multivariate analysis using the Kruskal–Wallis test. A p-value less than 0.05 were considered statistically significant. All analyses were performed using JMP v11.0 (SAS Institute Japan Inc., Tokyo, Japan).

Abbreviations

MG: myasthenia gravis; NMOSD: neuromyelitis optica spectrum disorders; Abs: autoantibodies; CNS: central nervous system; AQP4: Anti-aquaporin 4; LO-NMOSD: late-onset neuromyelitis optica spectrum disorders; VLO-NMOSD: very late-onset neuromyelitis optica spectrum disorders; EO-NMOSD: early-onset neuromyelitis optica spectrum disorders; EDSS: the expanded disability status scale; IVMP: intravenous methylprednisolone; PSL: Prednisolone; ANA: anti-nuclear antibody; RF: rheumatoid factor; IgG: immunoglobulin G; IRB: Institutional Review Board.

Declarations

Ethics approval and consent to participate

For a retrospective analysis that is Institutional Review Board (IRB) of Kumamoto University-approved (Permit Number: 1918), state that approval from an ethical standards committee to conduct this study was received.

Consent for publication

Not applicable.

Availability of data and materials

Anonymized data will be shared by request from any qualified investigator. All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Clinical features of patients with NMOSD

Features	Very late-onset (n = 7)	Late-onset (n = 11)	Early-onset (n = 26)	p-value
Males	2 (28.6)	3 (27.3)	3 (11.5)	0.389[a]
Age at onset, years	73.0 (72.0–77.0)	53.0 (51.0–56.0)	32.0 (25.0–40.5)	**≤ 0.001**[b]
Disease duration, months	3.0 (1.0–-11.0)	4.0 (1.0–5.0)	7.5 (4.0–19.25)	**0.015**[b]
Charlson comorbidity index	1 (0–3)	0 (0–1)	0 (0–1)	0.178 [b]
Onset symptoms				
Optic neuritis	2 (28.6)	7 (63.6)	16 (61.5)	0.257 [a]
Myelitis	6 (85.7)	4 (36.4)	13 (50.0)	0.116 [a]
Brainstem	1 (14.3)	1 (9.1)	0 (0)	0.193 [a]
Symptoms during the course				
Optic neuritis	2 (28.6)	7 (63.6)	21 (80.8)	**0.029** [a]
Myelitis	6 (85.7)	7 (63.6)	20 (76.9)	0.539 [a]
Brainstem	1 (14.3)	1 (9.1)	0 (0)	0.193 [a]
Time between first symptom and diagnosis of NMOSD, months	1 (1–41)	2 (1–3)	15 (2.5–216)	**0.012** [b]
Total number of attacks	1 (1–2)	1 (1–2)	2 (1–5.25)	**0.012** [b]
Attack interval, month	3.0 (2.0–25.4)	5.0 (2.0–53.0)	24.76 (10.80–55.14)	**0.046** [b]
Nadir EDSS score	8.5 (6.0–9.0)	5.0 (4.5–7.5)	5.75 (5–6.25)	0.083 [b]
EDSS score at last visit	6.0 (3.5–9.0)	4.5 (3.0–5.0)	5 (3.875–6)	0.243 [b]
Nadir Nurick scale	5.0 (5.0–5.0)	2 (0–5)	3 (0.75–5)	0.059 [b]
Nurick scale at last visit	3.0 (2.0–5.0)	2 (0–2)	2 (0–3)	0.107 [b]
Treatment of acute disease attacks				
PLEX	0 (0)	1 (9.1)	5 (19.2)	0.340 [a]
IAPP	3 (42.9)	4 (36.4)	7 (26.9)	0.675 [a]
IVIg	1 (14.29)	1 (9.1)	1 (3.85)	0.587 [a]

IVMP	7 (100)	11 (100)	26 (100)	-
Long-term treatment				
PSL	6 (85.7)	11 (100)	25 (96.2)	0.353 [a]
AZA	0 (0)	1 (9.1)	0 (0)	0.216 [a]
Tacrolimus	0 (0)	0 (0)	1 (3.9)	0.702 [a]

Data are presented as n (%) or median (interquartile range).

NMOSD, neuromyelitis optica spectrum disorders; EDSS, expanded disability status scale; PLEX, plasma exchange; IAPP, immunoadsorption plasma pheresis; IVIg, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; PSL, prednisolone; AZA, azathioprine.

[a] χ^2 test

[b] Kruskal–Wallis test

Table 2. Laboratory findings

	Very late onset (n=7)	Late onset (n=11)	Early onset (n=26)	p-value
AQP4 Abs-positive	7 (100)	10 (90.9)	24 (92.3)	0.729 [a]
ANA positive	3/7 (43)	3/10 (30)	7/12 (58)	0.422 [a]
Serum IgG (mg/dL)	983 ± 300	1060 ± 396	1080 ± 307	0.861 [b]
CSF analysis				
Cell, cells/μL	5 (1.75–11.25)	2 (1–11)	4.00 (2.00–7.75)	0.790 [b]
Protein, mg/dL	52.5 (39.5–101.175)	32 (28.3–42.0)	39.6 (30.9–68.4)	0.114 [b]
IgG (mg/dL)	3.8 ± 0.5	3.6 ± 2.1	6.8 ± 7.1	0.354 [b]
IgG index	0.66 ± 0.18	0.54 ± 0.14	0.60 ± 0.09	0.333 [b]

Data are presented as mean ± standard deviation, n (%), or median (interquartile range).

AQP4 Abs, anti-aquaporin 4 antibodies; ANA, anti-nuclear antibody; IgG, immunoglobulin G; CSF, cerebrospinal fluid.

[a] χ^2 test

[b] Kruskal–Wallis test

Table 3. MRI findings in the brain and spinal cord

	Very late onset (n=7)	Late onset (n=11)	Early onset (n=26)	p-value
Cerebrum	5 (71.4)	5 (45.5)	19 (73.1)	0.254 [a]
Cerebellum	0 (0)	0 (0)	0 (0)	-
Brainstem	3 (42.9)	2 (18.2)	8 (30.8)	0.523 [a]
Optic nerve	1 (14.3)	8 (72.8)	19 (73.1)	**0.013** [a]
Cervical spinal cord	4 (57.1)	5 (45.5)	14 (53.9)	0.862 [a]
Thoracic spinal cord	6 (85.7)	5 (45.5)	18 (69.2)	0.183 [a]
Lumbar spinal cord	1 (14.3)	0 (0)	1 (3.4)	0.353 [a]
Length of spinal lesion, VBs	8 (3–11)	1 (0–3)	4 (1.75–6)	**0.038** [b]

Data are presented as n (%) or median (interquartile range).

VB, vertebral body

[a] χ^2 test

[b] Kruskal–Wallis test

Figures

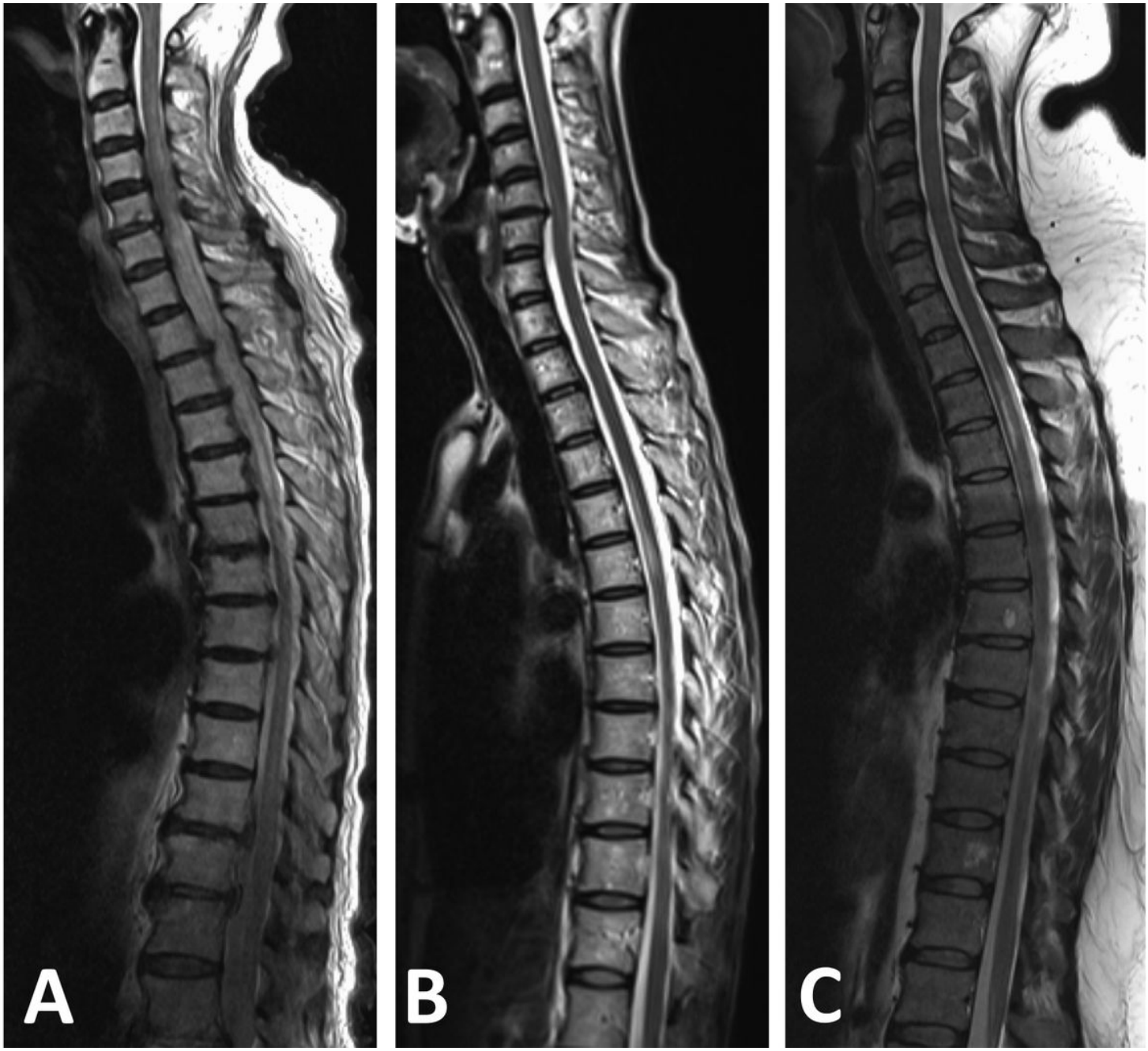

Figure 1

T2-weighted sagittal spinal MRIs of patients with VLO-NMOSD, LO-NMOSD, and EO-NMOSD A: An 81-year-old woman with progressive paraparesis and blindness in both eyes. Spinal MRI revealed a long cord lesion at C2–T5. CSF analysis revealed pleocytosis (16 per μl) and increased protein (84.0 mg/dl). Serum test for AQP4 Abs was positive. B: A 56-year-old woman with right-sided dysesthesia below T6, and reduced vision in both eyes. Spinal MRI revealed a long cord lesion at T4–T6 and T7-T8. CSF analysis revealed normal cell counts and protein. Serum test for AQP4 Abs was positive. C: A 36-year-old woman with bilateral dysesthesia below T5, and blindness in the left eye. Spinal MRI revealed a long cord lesion at T3–T8. CSF analysis revealed normal cell counts and increased protein (69.7 mg/dl). Serum test for AQP4 Abs was positive. VLO-NMOSD, very late-onset neuromyelitis optica spectrum disorders; LO-

NMOSD, late-onset neuromyelitis optica spectrum disorders; EO-NMOSD, early-onset neuromyelitis optica spectrum disorders; CSF, cerebrospinal fluid; AQP4 Abs, aquaporin-4 antibodies