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Gender differences among Chinese patients with neuromyelitis optica spectrum disorders

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ABSTRACT

Background: *Neuromyelitis optica* spectrum disorders (NMOSD) are autoimmune, inflammatory demyelinating diseases of the central nervous system, which have established variations in prevalence across different ethnicities and genders. The objective of this study was to investigate differences in clinical features among men and women with NMOSD, according to the 2015 diagnostic criteria.

Methods: A total of 97 patients with NMOSD were recruited from inpatient neurology clinics in this retrospective study. Demographic and clinical data were extracted from the various databases. Data on epidemiology, clinical signs, initial symptoms, and laboratory indices of men and women with NMOSD were compared.

Results: The cohort of this study had a female/male ratio of 5.47:1, with annualized relapse rates of 0.72 in female and 0.56 in male patients. Among female patients, 29.2% and 53.6% initially experienced acute optic neuritis and acute myelitis, respectively, while the prevalence of these symptoms was 46.6% and 53.3% among male patients. A total of 14.6% and 2.4% of female patients had area postrema symptoms and other brainstem signs, respectively on study enrollment. The prevalence of anti-AQP4-autoantibodies and anti-thyroid peroxidase autoantibodies/anti-thyroglobulin autoantibodies (TPO/TG-Ab) was significantly higher among women (77% and 45.7%) than among men (46.1% and 13.3%) ($P < 0.05$ for both comparisons). A total of 11 women with NMOSD (11.3% of the cohort) also had autoimmune diseases.

Conclusions: Women with NMOSD have higher morbidity levels than men with this disease and are more likely to have autoimmune diseases and brainstem lesions, especially in the area postrema.

1. Introduction

Neuromyelitis optica (NMO), also known as Devic's disease, and related spectrum disorders (NMOSD), describes an idiopathic inflammatory demyelinating and necrotizing disease, characterized by simultaneous inflammation and demyelination of the optic nerves and spinal cord. Some, but not all patients with NMOSD have anti-aquaporin-4 (AQP4) immunoglobulin G autoantibodies (AQP4-Ab), and the presence of these autoantibodies has been used in the differential diagnosis of NMO since 2006 (Wingerchuk et al., 2007). In a cohort of 106 patients with AQP4-Ab-positive NMOSD in the United Kingdom or Japan, the majority of patients (87%) were female; however, data from this study indicated that male patients with NMOSD are more likely to have visual deterioration to the point of reaching visual disability compared with female patients (Kitley et al., 2012). Furthermore, the ratio of female/male patients reported in this study relates only to those with serologically confirmed AQP4-Ab. Data from many studies indicate that patients with AQP4-Ab-negative NMOSD, or those of unknown AQP4-Ab status have a similar clinical course of disease; therefore, patients with AQP4-Ab-negative or those of unknown AQP4-Ab status often receive the same treatments as those with AQP4-Ab-positive NMOSD, and many will eventually develop typical NMO. Thus,

Abbreviations: NMOSD, neuromyelitis optica spectrum disorder; TPO-Ab, anti-thyroid peroxidase autoantibodies; TG-Ab, anti-thyroglobulin autoantibodies; AQP4, aquaporin-4; AQP4-Ab, anti-aquaporin-4 (AQP4) immunoglobulin G autoantibodies; PLA, People's Liberation Army; ANA, anti-nuclear antibodies; anti-dsDNA, anti-double-stranded DNA; ELISA, enzyme-linked immunoassay; ENA, extractable nuclear antigen; SSA, anti-Sjögren's-syndrome-related antigen A antibodies; SSB, anti-Sjögren's-syndrome-related antigen B antibodies; UIRNP, anti-U1 ribonucleoprotein; Scl-70, anti-topoisomerase I; Jo-1, anti-histidyl tRNA synthetase; A-β2-GPI, anti-β_2 glycoprotein I; ACL, anti-cardiolipin antibodies; MOG-Ab, anti-myelin-oligodendrocyte glycoprotein autoantibodies

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in 2015, the International Panel for NMO Diagnosis published revised diagnostic criteria for NMOSD (Wingerchuk et al., 2015). The new diagnostic criteria suggested further patient stratification by serological subtype testing (NMOSD with, or without AQP4-Ab). The updated core clinical characteristics required for patients with AQP4-Ab, include clinical syndromes or MRI findings related to optic nerve, spinal cord, area postrema, other brainstem, diencephalic or cerebral presentations.

The introduction of new diagnostic criteria has improved the sensitivity of definitive diagnosis and is conducive to immunological interventions at an early stage in the clinical course of NMOSD. However, whether or not these criteria have any effect on the ratio of female/male with NMOSD remains unclear. The first aim of this study is to investigate whether the ratio of female/male patients with NMOSD has been influenced by the introduction of the new criteria. Secondly, we aim to gain insight into the differences in clinical features between male and female patients with NMOSD.

2. Methods

2.1. Participants

A total of 97 patients inpatients were consecutively enrolled in this study between January 2013 and December 2015 at the Neurology Department, Chinese People's Liberation Army (PLA) General Hospital. Demographic and clinical data were extracted from the databases, including age, age at onset of NMOSD, disease duration and clinical manifestation at onset of disease. NMOSD was diagnosed by two treating neurologists, according to the International Consensus Diagnostic Criteria for NMOSD (Wingerchuk et al., 2015). Patients diagnosed with Sjögren's syndrome all met the American College of Rheumatology classification criteria for Sjögren's syndrome (Shiboski et al., 2012). Patients diagnosed with Hashimoto's thyroiditis all met the criteria outlined in the Chinese diagnosis and treatment guidelines for thyroid disease (Association, 2008).

2.2. Measurement of serum antibody levels

Venous blood samples were collected from each patient and sent to the laboratory of the Rheumatology Department at the PLA General Hospital, for screening of serum antibody levels by technicians who were blinded to the clinical diagnosis. Serum AQP4-Ab were detected by investigators who were blinded to the diagnosis using indirect immunofluorescence staining of cells transfected with human AQP4 protein, a method reported to be more sensitive than the original NMO-IgG assay (this analysis was conducted at the Peking Union Medical College Hospital, Beijing, China). An indirect immunofluorescence assay (Euroimmun Medical Laboratory Diagnostics Stock Company, Beijing, China) with a cutoff value for a positive titer of 1:160 was used for the detection of anti-nuclear antibodies (ANA). A dot-immunogold filtration assay with an imprinting banding technique was used to detect anti-double-stranded DNA (anti-dsDNA) antibodies (Euroimmun Medical Laboratory Diagnostics Stock Company), and an enzyme-linked immunoassay (ELISA) dot technique was used for the detection of the extractable nuclear antigen (ENA) spectrum of polypeptide antibodies, including anti-Sjögren's-syndrome-related antigen A antibodies (SSA), anti-Sjögren's-syndrome-related antigen B antibodies (SSB), anti-U1 ribonucleoprotein (UIRNP), anti-Smith-antibodies, anti-topoisomerase I (Scl-70), and anti-histidyl tRNA synthetase (Jo-1) (Euroimmun Medical Laboratory Diagnostics Stock Company). An ELISA dot technique was used for the detection of cardiolipin, including anti-β_2 glycoprotein I (A-β2-GPI) and anti-cardiolipin (ACL) antibodies (Euroimmun Medical Laboratory Diagnostics Stock Company). A chemiluminescent technique was used for the detection of anti-thyroid-peroxidase and anti-thyroglobulin antibodies (Siemens limited company). Note that in this paper, the term ‘ANA’ is used specifically to describe the detection of the ANA antibodies using an indirect immunofluorescence assay, while the term ‘ANAs’ is used as a collective term for all ANAs assayed in this study, including ANA, ACL, anti-dsDNA, and the various anti-ENA antibodies.

2.3. Statistical analysis

All analyses were performed using Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) software, version 20. Differences between groups were analyzed using a chi-squared or Fisher's exact test for comparisons of binary and categorical data, respectively. A P value of < 0.05 was considered statistically significant.

3. Results

3.1. Demographics

Among the 97 patients with NMOSD enrolled in this study, 82 (84.5%) were female and 15 (15.5%) were male (female/male ratio 5.47:1). Female patients with NMOSD had a mean age at disease onset of 36.2 ± 14.2 years (range: 14.1–66.9 years) and the median time since disease onset was 25 (7.2–57.6 months), while the male patients had a mean age at diagnosis of 41.3 ± 16.0 years (range: 18.6–66.5 years), and a median duration of 15.6 months (4.3–58.8 months) (Table 1).

3.2. Annualized relapse rate

A total of 72 female patients (87.8% of all female study participants) had relapsing NMOSD; these patients had between one and 17 relapses, with a median of two relapses per patient, and an average annualized relapse rate of 0.72. A total of 10 male patients (66.7%) had relapsing NMOSD, these patients had between one and five relapses, with a median of two relapses per patient, and an average annualized relapse rate of 0.56. No statistically significant differences in the average annualized relapse rates were observed between the two groups.

3.3. Initial presentation

The six core clinical characteristics upon presentation of the patients included in this study are described in Table 2. A total of 46.6% of male patients initially presented with acute optic neuritis and 53.3% presented with acute myelitis as initial symptoms, while the prevalence of such symptoms upon initial presentation in female patients was 29.2% and 53.6%, respectively. A total of 14.6% of female patients initially presented with area postrema lesions as the initial symptom, although this presentation was not observed in any of the male patients included in this study. All 12 of the patients presenting with area postrema lesions initially underwent gastroenterological evaluation, owing to the nausea and vomiting associated with such lesions.

3.4. Distribution of autoantibodies and disorders

A significantly greater proportion of female patients (77.0%) were found to be positive for AQP4-Ab, compared with 46.2% of male patients ($P < 0.05$). Furthermore, 45.7% of women had detectable anti-thyroid-peroxidase (TPO) and/or anti-thyroglobulin (TG)

Table 1
The demography difference between male and female NMOSD.

	Female (n = 82)	Male (n = 15)	p value
Age onset (y)	14.1 ~ 66.9	18.6 ~ 66.5	0.209
Mean age onset (y)	36.2 ± 14.2	41.3 ± 16.0	0.264
Course of disease (y)	2.1 (0.6 ~ 4.8)	1.3 (0.6 ~ 4.9)	0.323
The relapse proportion	72 (89.9%)	10 (66.7%)	0.037

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