A multi-facet comparative analysis of neuromyelitis optica spectrum disorders in patients with seropositive and seronegative AQP4-IgG

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Abstract
Introduction: Neuromyelitis optica spectrum disorders (NMOSD), a rare, serious, demyelinating disease of the central nervous system (CNS), is associated with immunoglobulin G (IgG) antibodies targeting aquaporin-4 (AQP4-IgG). This study retrospectively analyzed the clinical features of 67 patients. 49 and 18 of 67 cases (male/female: 11/56) were AQP4-IgG (+) and AQP4-IgG (−), respectively. The initial symptoms were optic neuritis [n=34, AQP4-IgG (+)/−: 31/3], myelitis [n=18, AQP4-IgG(+)/−: 13/5], co-occurrence of ON and myelitis [n=15, AQP4-IgG (+)/−: 5/10].

Conclusions: There was no statistically significant difference between the 2 groups in terms of ages, and magnetic resonance imaging findings, but the patients had a significant difference (P < .05) in sex, the course of disease and Expanded Disability Status Scale (EDSS) scores after drug treatment. Patients with AQP4-IgG (−) are likely to have a better prognosis and a favorable monophasic course.

Abbreviations: ADEM = acute disseminated encephalomyelitis, AQP4 = immunoglobulin G (IgG) antibodies targeting aquaporin-4, CNS = central nervous system, EDSS = Expanded Disability Status Scale, MRI = magnetic resonance imaging, MS = multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorders.

Keywords: AQP4-IgG, clinical features, neuromyelitis optica spectrum disorders

1. Introduction

Neuromyelitis optica spectrum disorders (NMOSD; also known as Devic’s disease) is a rare but serious autoimmune-related demyelinating disease of the central nervous system (CNS) that mainly affects the optic nerves and spinal cord with high recurrence rate, and usually misdiagnosed as multiple sclerosis (MS) or acute disseminated encephalomyelitis (ADEM).[1–3] This disease has been described for a century or more before the discovery of the highly specific autoantigen of immunoglobulin G (IgG) antibodies targeting aquaporin-4 (AQP4) which regulates water homeostasis.[4–5] It has a striking female preponderance of 9:1, of which 80% to 90% have relapsing course, and 10% to 20% patients have monophasic course.[1–3]

Previous studies have demonstrated the association between NMOSD and the presence of AQP4-IgG, but the possible different clinical features in patients with seropositive or seronegative NMOSD are not well defined. In this study, we divided patients with NMOSD into AQP4-IgG positive (+) and AQP4-IgG negative (−) groups by the serologic test and made a comparative analysis of them to improve the clinical recognition for physicians.

2. Methods

2.1. Patients

This study was carried out in People’s Hospital of Zhengzhou University. We retrospectively reviewed the electronic medical records of 95 patients from September 2015 to November 2016. All patients met the diagnosis of NMOSD according to the international consensus diagnostic criteria described as below. Patients were divided into AQP4-IgG (+) and AQP4-IgG (−) groups. To compare the disorders of the 2 groups, demographic data, clinical information, laboratory studies, image findings, drug treatment, and clinical efficacy, and the score of Expanded Disability Status Scale (EDSS) were carefully reviewed by 3 experienced investigators to ensure accurate diagnosis.

2.2. Laboratory test

Serology tests were carried out before treatment, including the detection of AQP4-IgG antibody, thyroid hormone...
determinations, extractable nuclear antigen (ENA) autoantibodies or more.

### 2.3. Magnetic resonance imaging (MRI)

Brain and spinal cord MRI were performed using a uniform protocol, including T1-weighted images, T2-weighted images, sagittal T1-weighted, and fluid-attenuated inversion recovery (FLAIR) images.

### 2.4. Inclusion/exclusion criteria for NMOSD

Patients must meet the diagnosis of NMOSD according to the international consensus diagnostic criteria. Patients with incomplete clinical data, uncertain diagnosis, critical illness, mortality, or missing follow-up data were excluded.

### 2.5. Statistics

All data were analyzed using IBM SPSS Statistics Base 22.0. Categorical data were compared by the Chi-square test. The Mann–Whitney U test and t test analysis were used when appropriate. Quantitative data were expressed using median (range) or mean ± standard deviation (SD). Using Shapiro–Wilk test to verify its normal distribution, if passing, statistical significance was considered as P < .05.

### 3. Results

#### 3.1. Demographic characteristics of the patients

Of the 95 patients who were initially diagnosed with NMOSD, 28 patients were later excluded. Among the 67 inclusions, 49 (73.1%, male/female: 3/46, mean age: 40.5 ± 16.7) are seropositive, and 18 (26.9%, male/female: 8/10, mean age: 38.5 ± 18.6) are seronegative (Table 1). There is no significant difference in age between the AQP4-IgG (+) patients and the AQP4-IgG (−) patients (P = .68 > .05) (Table 1).

#### 3.2. Clinical presentations

Among the 67 inclusions, patients present with optic neuritis (ON) [n = 34; AQP4-IgG (+)/(-): 31/3], isolated myelitis [n = 18; AQP4-IgG (+)/(-): 13/5], co-occurrence of ON and myelitis [n = 15; AQP4-IgG (+)/(-): 5/10]. Other initial symptoms include extremity weakness (n = 21), backache (n = 5), neck pain (n = 2), upper limb pain (n = 1), dizziness (n = 3), hiccup (n = 1), and diplopia (n = 2). In addition, nonspecific symptoms including dysphagia, ataxia and autonomic dysfunction were also found in several patients. Although it seems that motor symptoms were more common in the AQP4-IgG (−) group, there was no significant difference in onset of optic neuritis between them (Table 1).

#### 3.3. MRI findings

Of the 67 patients [AQP4-IgG (+)/(-): 49/18], the MRI abnormalities signals in AQP4-IgG (+) group was 5.30 ± 5.96 and was 5.28 ± 3.63 in AQP4-IgG (−) group. There was no statistically significant difference in MRI findings between the 2 groups (Table 1). The characteristic MRI manifestation in the AQP4-IgG (+) patients showed in Figure 1. The MRI manifestation in the AQP4-IgG (−) patients showed in Figure 2.

#### 3.4. Baseline rates of comorbidities in NMOSD

18 cases were complicated with suspicious autoimmune diseases, including autoimmune thyroid disease (n = 6), sjogren syndrome (n = 4), rheumatoid arthritis (n = 4), systemic lupus erythematosus (n = 1), myasthenia gravis (n = 1), or abnormal autoantibodies without clinical features (n = 2). Compared with the AQP4-IgG (−) group, the ratio of co-existing autoimmune disorders was higher in the AQP4-IgG (+) group (Table 1).

#### 3.5. Treatment and outcome

66 cases were treated with methylprednisolone boli (500 mg QD × 3). After the therapy, the EDSS score of AQP4-IgG (+) group was 2.2 ± 1.3 and the AQP4-IgG (−) group was 1.6 ± 0.6, the difference was statistically significant (P < .05). 1 case was treated with nutrients with no improvement. The median duration of the 2 groups were 3.1 ± 3.6 years and 1.2 ± 2.9 years, respectively, which have significant difference (P = .04). The rate of AQP4-IgG (+) in the monophasic and recrudescent course patients was 28.6% and 71.4%, respectively, the difference is statistically significant (Table 1).

### 4. Discussion

NMOSD is an inflammatory, demyelinating syndrome of the CNS with the discrete, relapsing characters. Moreover, NMO-IgG, an autoantibody, especially attacks the AQP4 expression zone, especially the surrounding ventricular, which may induce corresponding clinical manifestations, such as ON or myelitis. Population-based studies have described that 0.05 to 0.4 per
100,000 patients are AQP4-IgG (+), and this accounts for half of the clinical diagnosis of people with NMOSD.\textsuperscript{[10,11]} An extensive literature showed that NMOSD may occur in any age, and in both sexes, but it has a postpubertal female preponderance.\textsuperscript{[1,12]} Patients with co-existing autoimmune disorders may strengthen confidence about an NMOSD diagnosis. Since NMOSD has a high recurrence rate, disability rate, and disease burden and there may exist clinical differences between seropositive and seronegative patients, it is important to have a correct recognition.

We compared the clinical features of patients with AQP4-IgG (+) (n = 49, 73.1%) and AQP4-IgG (−) (n = 18, 26.9%) who had a clinical diagnosis of NMOSD.\textsuperscript{[6]} Our study results suggest that patients with seropositive antibody tended to have a postpubertal female preponderance, single part involvement (ON or myelitis), autoimmune disorders coexistence, longer duration of symptoms, poor prognosis and polyphasic course. Statistical analysis showed that these differences between the 2 groups were significant (P < .05), but there was no difference in onset age and MRI lesions between the 2 groups (P > .05).

However, this study has several limitations as follows. First, we used indirect immunofluorescence to detect only AQP4-IgG antibody without other methods and antibodies. Second, there is a lack of within-group comparison in this study, including ages and clinical symptoms. Third, this study did not compare NMOSD with other demyelinating disease of CNS, such as MS and ADEM. Additionally, this study may have some limitation such as small sample sizes and short-term follow-up.

Compared with AQP4-IgG (+) group, patients with AQP4-IgG (−) are likely to have a better prognosis and a favorable monophasic course. This reveals that AQP4 antibody not only can distinguish NMOSD from other diseases, but also may help to predict the patients who are at risk of recurrent, and could guide decisions regarding diagnostic and therapeutic strategies.

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