Retrospective study on effect of rheumatic immune related antibodies on clinical manifestation and cerebrospinal fluid characteristics of neuromyelitis optic spectrum disorders

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Abstract

Objective: To investigate that how the effect of rheumatic immune antibodies on clinical manifestation and cerebrospinal fluid characteristics of neuromyelitis optic spectrum disorders (NMOSD). Methods: All 35 patients with NMOSD in the Second Hospital, Cheeloo College of Medicine, Shandong University from 2017 to 2019 were retrospectively reviewed. All patients underwent examination of serum ANA, dsDNA, SS-A, SS-B,Ro-52 , AMA M2, Jo-1, PM-Scl, Scl-70, Sm and et al. 6 positive-autoantibody patients are compared with 29 negative-autoantibody patients in gender, onset age, duration, number of attacks, EDSS, initial presentation (on, spinal cord or brain), CSF WBC, protein, Oligoclonal band and MBP. Results: The 6 NMOSD patients with all AQP4-IgG positive had positive autoantibodies (17.1%), with no diagnose as CTD. The frequency of SSA in the positive group was 50%, while Ro-52 was 75%, AMA-M2 was 33%, ANCA-PR3 was 17%, and AHA was 17%. They were significantly higher in NMOSD patients with auto-immune antibodies positive than those without auto antibodies ($P<0.05$). EDSS scores were positively correlated with two groups (NMOSD with or without auto antibodies). The positive group had much more EDSS scores than the negative group. The number of CSF cells in positive group was basically in normal range, median was 2.5x106. Median of CSF protein was 866mg/L, which was much higher than negative group. Conclusions: NMOSD patients with positive autoantibodies tends to be more frequent in the patients with AQP4-IgG, who have more severe intrathecal autoimmune inflammatory and disability. So they might need more intensive treatment in the future.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory autoimmune disease of the central nervous system. It is characterized by recurrent episodes of myelitis and optic neuritis and less frequently brainstem and cerebral involvement[1]. NMOSD is a relapsing neurological illness sometimes reported with primary SS、SLE and other connective tissue diseases. And almost all connective tissue diseases (CTD) and related disorders can be complicated by various neuropsychiatric syndromes[2]. But these patients are not diagnosed as CTD. Some researchers explained this phenomenon as immune generalization in autoimmune disorders.

Antinuclear antibody, ds-DNA, SS-A, SS-B,Ro-52 are common auto-immune antibodies in autoimmune disease. NMOSD is often related with these antibodies and needed to make differential diagnosis with CTD, such as Sjogren's syndrome,Systemic lupus,Systemic vasculitis,erythematosus and et al[3]. NMOSD is a distinct autoimmune condition that may co-occur with SLE or other autoimmune diseases such as acute demyelinating encephalomyelitis (ADEM) and Behcet's disease, that these infections or autoimmune diseases maybe the trigger for NMOSD, but a real pathophysiological association remains unknown.

In this study, we reviewed all the records of NMOSD patients from 2017 to 2019 admitted to the second

hospital of Cheeloo College of Medicine. Our study comes to shed light and strengthen the fact that link between auto-immune antibodies and NMOSD.

Materials and Methods

Patients

Patients with NMOSD were recruited from the second hospital, Cheeloo College of Medicine, Shandong University, from January 2017 to December 2019. NMOSD was diagnosed according to the 2015 international consensus diagnostic criteria for NMOSD[4]. And CTD was diagnosed by rheumatologists according to published criteria and typology guidelines (e.g., SLE, SS, rheumatoid arthritis (RA), or undifferentiated CTD (UCTD)[5]). All patients were tested for AQP4-IgG (by cell-based assays), myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG), autoreactive antibodies (ANAs), and extractable nuclear antigen autoantibodies (ENAs). Spinal and brain MRI were available before treatment. NMOSD patients with auto-immune antibodies positive were not diagnosed as CTD by rheumatic immune clinic. Clinical characteristics, including gender, age, disease duration, number of attacks, MRI information, and EDSS disability score during attack and remission were prospectively recorded. A relapse was defined as a new neurological symptom lasting at least 24 h and accompanied by new neurological examination finding and new lesions on MRI. The clinical remission was defined as both neurological symptoms and neurological examination signs that remained stable for at least 30 days from last relapse. Number of cases is 35 (female: male=28:7), onset age is from 18 to 75. Median age is 49.63±12.03. Disease duration (month) is 46.90(1-396).

The study was approved by the Ethics Committee of the second hospital, Cheeloo College of Medicine, Shandong University and written informed consent was obtained from each participant.

Laboratory testing

Blood and cerebrospinal fluid (CSF) samples were obtained from all the patients in our study during hospital admission. AQP4-IgG detected by cell-based assay (CBA) and CSF oligoclonal banding (OCB) were conducted in Guangzhou kingmed Diagnostics and Hangzhou DIAN Medical Laboratory,CSF cell counts and protein were conducted in our clinical neuroimmunological laboratory. Tests for auto antibodies (ANAs, ENAs, RF and ANCAs), immunoglobulins, and complement were conducted, along with other serological profiling, in the immunology and clinical laboratory of our hospital.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 22.0). All quantitative data in this study were presented as the mean+-standard deviation (SD) or the median and range. Values of p = 0.05 were considered statistically significant. Quantitative data were processed using the Mann–Whitney U-test or Student's t-test.

Results

From 2017 to 2019, a total of 35 patients satisfied the diagnostic criteria for inclusion in this study: 29 NMOSD patients without auto-immune antibodies and 6 with auto-immune antibodies(including 6 with ANA,3 with SSA,4 with Ro-52,2 with AMA-M2,1 with ANCA-PR3,1 with AHA). NMOSD patients with auto-immune antibodies were not diagnosed as CTD by rheumatic immune clinic. The clinical features and laboratory findings of the NMOSD patients with auto-immune antibodies positive are summarized in Table 1. The result shows that 6 NMOSD patients(female: male=5:1)with auto-immune antibodies positive have some special features. Onset age is from 18 to 75. Median age is 50.17+-20.82. Disease duration (month) is 114.17.There is 15 patients belong to polyphasic courses, while others belong to monophasic course. Among the 6 patients with auto-immune antibodies, they were not diagnosed as CTD by rheumatic immune clinic. The demographic and clinical features of the patients are summarized in Table 2. NMOSD patients with auto-immune antibody positive had higher EDSS scores、number of attacks、disease duration and more severe sensory disability at nadir than patients without auto-immune antibody (P<0.05). Optic nerve and spinal cord are more likely to be involved meanwhile in those positive. In Table 2, we can see that there

is one case whose first symptom was on, accounting for 16.7%; there are 4 cases whose first symptom was myelitis, accounting for 66.7%; there is one case whose first symptom was both on and myelitis, accounting for 16.7%. In the negative group, there are 6 cases whose first symptom was on, accounting for 20.7%; there are 19 cases whose initial presentation was myelitis, accounting for 66.5%; 2 cases both on and myelitis was accounting for 6.9%. There was no brainstem lesion of MRI in positive group. In the negative group, there was one case of polar posterior region syndrome, accounting for 3.4%.

CSF features were summarized in Table 3, CSF cells of positive group was basically in normal range, median was $2.5x10^6$, CSF protein was high, and median was 866mg/L. No oligoclonal banding and MBP were detected in positive group. In 29 cases of negative group, median of CSF cells was 16.17×10^6, CSF protein was normal, median was 282.7mg/l, oligoclonal banding (OCB) was positive in one case, accounting for 3.4%, MBP was positive in 2 cases, accounting for 6.9%.

Discussion

Neuromyelitis optica spectrum disorders (NMOSD) are relapsing inflammatory conditions of the CNS presenting with ON and LETM as key clinical features[6]. Many autoimmune antibodies may be produced in development of NMOSD because of immune reaction generalization. Only when the antibody reaches a certain degree, the damage may occur and clinical symptoms may appear. There may be a certain amount of autoantibodies without any clinical manifestations.

48% of NMOSD were detected auto-immune antibodies positive by Wingerchuk [7]. In our research, there is 17% NMOSD and patients with AQP4-IgG positive are more likely to be associated with non organ specific autoantibody. But there is no sign of systemic autoimmune disease, and the immune response of these patients may be more extensive, which was similar to Pittock[8].

Although the frequency of ANAs was significantly higher in NMOSD patients with auto-immune antibodies positive than those without antibodies in our study, the frequency of ANAs in positive group was 100%(from 1:100 to 1:1000), which was similar to the frequencies reported in other reports[9]. The frequency of SSA in the latter group was 50%, while Ro-52 was 75%, AMA-M2 was 33%, ANCA-PR3 was 17%, and AHA was 17%. They were significantly higher in NMOSD patients with auto-immune antibodies than in those without auto antibodies ($P<0.05$). The negative group had much more EDSS scores. NMOSD patients with positive autoantibodies tends to be more frequent in patients with AQP4-IgG, who have more severe intrathecal autoimmune inflammatory and disability. So they might need more intensive treatment. However, of the 6 NMOSD patients with auto-immune antibody positive in our study, none developed CTD before NMOSD, and in the other 29, no auto-immune antibody followed the diagnosis of NMOSD, which was similar to previous report[10].

We will recruit more NMOSD patients and lead to a deeper understanding of auto-immune antibody in NMOSD. Meanwhile, we also need to follow up to investigate whether they will develop into CTD.

Conflict of Interest

The authors declare no conflict of interest.

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