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Research Article

Clinical Outcomes of Neuromyelitis Optica with Brain Magnetic Resonance Imaging Abnormalities

Abstract

Objective: To investigate clinical outcomes of neuromyelitis optica (NMO) patients with brain magnetic resonance imaging (MRI) abnormalities.

Methods: One hundred and thirty-seven patients with NMO were enrolled. Clinical, laboratory, and MRI features were assessed and compared according to different distribution patterns of brain lesions.

Results: The relapse number, Expanded Disability Status Scale (EDSS) score at initial diagnosis, and EDSS score at last visit were significantly higher in NMO patients with brain abnormalities than those in NMO patients without brain abnormalities, respectively. NMO patients with brainstem involvement had higher relapse number, EDSS score at initial diagnosis, and EDSS score at last visit than those without brain abnormalities or with only suprotentorial lesions.

Conclusions: Appearance of brain abnormalities in the initial stage, especially brainstem involvement, might be a predictor of severe neurologic deficits and poor prognosis in NMO.

Introduction

Neuromyelitis optica (NMO), also known as Devic syndrome or Devic's disease, is an idiopathic demyelinating and inflammatory disease that preferentially involve the optic nerve and spinal cord. The 1999 Wingerchuk criteria for NMO required no evidence of clinical disease outside the optic nerve or spinal cord as an absolute criterion and negative brain magnetic resonance imaging (MRI) at onset as a supportive criterion [1]. As NMO-IgG was found to be a specific autoantibody marker for NMO [2] and many studies reported incidences of abnormalities in the brain MRI of NMO [3-10], The diagnostic criteria for NMO were revised in 2006 and brain MRI lesions were not considered as an excluding criteria as long as they did not fulfill the diagnostic criteria for multiple sclerosis (MS) [11].

It has been reported that the brain lesions in NMO could cause clinical symptoms and signs [12]. However, it is unclear whether the clinical outcomes of NMO patients with brain MRI abnormalities were different from those without brain MRI abnormalities. Therefore, we investigated the clinical outcomes of NMO patients with brain MRI abnormalities.

Methods

Ethics statement

This research was approved by the ethics committee of the Third Affiliated Hospital of Sun Yat-sen University. All participants involved in this study provided written informed consent.

Patients

Our database comprised 137 patients with NMO who were diagnosed and admitted from August 2005 to July 2013 in the MS Center of the Third Affiliated Hospital of Sun Yat-sen University. NMO was diagnosed according to the 2006 Wingerchuk criteria [11]. All of the patients received high-dose corticosteroids (intravenous methylprednisolone 1 g per day for 5 days) during the acute period, another course of high-dose corticosteroids therapy would be given if no obvious recovery was attained. For steroid-refractory patients, plasma exchange or intravenous immunoglobulin were applied. Small dose of prednisone combined with azathioprine was used for prevention of relapse. All of the patients were followed up in the outpatient department once a month after discharge. Clinical data and MRI scans were collected from these consecutive patients.

Serums from all patients were tested for anti-AQP4 antibody by a commercial sampling kit (Euroimmun, Germany) according to the manufacturer's instructions. Laboratory tests were performed in all cases to exclude infectious diseases, connective tissue diseases, vascular diseases and metabolic disorders.

MRI scanning

Brain and spinal cord MRI scans were performed in all patients within two weeks after onset of demyelinating events, using a GE 1.5T MR scanner (General Electric, Milwaukee, Wisconsin, USA). The slice thickness of the axial scans was 5 mm. Conventional MRI protocols were used in all patients: T1-weighted images (T1WI) with and without gadolinium enhancement (400/15.5 ms, TR/TE) and T2-weighted images (T2WI) (2500–3500/100 ms, TR/TE) for spinal cord MRI; and T1WI with and without gadolinium enhancement (2128–2300/11.6–12.4 ms, TR/TE), T2WI (4600–4640/97.8–102 ms, TR/TE), and fluid-attenuated inversion recovery (FLAIR) (8800/120 ms, TR/TE) for brain MRI [13]. Each patient underwent MRI scanning at the time of the initial diagnosis, prior to corticosteroid treatment.

No patients were receiving immunomodulatory treatment at the time of the MRI scanning. Brain abnormalities including nonspecific brain lesions and specific brain lesions were assessed with T2-FLAIR sequences. The longitudinally extensive transverse myelitis (LETM) lesion in spinal cord was defined as involvement of three or more vertebral segments [11]. All of the MRI scans were analyzed by an experienced neuroradiologist and a neurologist. The numbers and locations of the brain MRI lesions as well as the length and locations of the spinal cord MRI lesions were recorded. The final assessments were made by consensus.

Statistical analysis

Statistical analysis was performed by SPSS version 17.0. Values of $p<0.05$ were considered statistically significant. Quantitative data were processed using the Mann–Whitney U-test, one-way analysis of variance (ANOVA), rank of one-way ANOVA, or pairwise comparison among groups with the least significant difference (LSD) test (level of test $p=0.05$). All quantitative data in this study are presented as mean±standard deviation (SD) or median±range. Qualitative data were analyzed with the χ^2 test or Fisher's exact test.

Results

The clinical, laboratory, and MRI features of the NMO patients with and without brain abnormalities are summarized in Table 1. The incidence of brain MRI abnormalities in the patients with NMO was 75.2% (103/137) in our study. There were no statistical differences in female/male ratio, ages at onset, disease duration, and time of follow-up between these two groups. The relapse number was significantly higher in NMO patients with brain abnormalities (Group B) than that in NMO patients without brain abnormalities (Group A) ($p=0.002$). The Expanded Disability Status Scale (EDSS) score at initial diagnosis of Group B was higher than that of Group A with a marginally significant difference ($p=0.042$). And the EDSS score at last visit of Group B was significantly higher than that of Group A ($p=0.001$).

No statistical difference was found in NMO-IgG seropositivity between these two groups.

The segments of spinal cord MRI lesions and percentage of patients with LETM in these two groups were similar. Further analysis showed that the segments of cervical cord MRI lesions in Group B were longer than those in Group A, but did not reach significant difference. And the segments of thoracic cord MRI lesions in Group A were significantly longer than those in Group B ($p=0.030$). Since there was only one patient with spinal cord MRI lesion outside the cervical and thoracic cord, we did not set up other subsets for spinal cord MRI.

In order to find out which brain region was associated with higher relapse number and EDSS score in patients with NMO, we further classified these patients into four groups according to the distribution of the brain lesions: patients without brain abnormalities (Group 1), patients with only supratentorial lesions (Group 2), patients with only brainstem lesions (Group 3), and patients with both supratentorial and brainstem lesions (Group 4). Since there was only five patient with cerebellar lesions, we did not set up other groups according to cerebellum involvement. All the five patients were coexistent with both supratentorial and brainstem lesions, so they were included in Group 4.

The clinical, laboratory, and MRI features of these four groups are summarized in Table 2. There were no statistical differences in female/male ratio, ages at onset, disease duration, and time of follow-up among these four groups. The relapse number and EDSS score at last visit of Group 2 were higher than those of Group 1, respectively, but none of them reach significant difference. No statistical difference was found in EDSS score at initial diagnosis between Group 1 and Group 2. The relapse number, EDSS score at initial diagnosis, and EDSS score at last visit of Group 3 were significantly higher than those of Group 1, respectively ($p=0.008$, 0.016 and 0.001, respectively). The relapse number of Group 3 was higher than that of Group 2, but did

Table 1: Clinical, laboratory, and MRI features of the NMO patients with and without brain abnormalities.

	Group A (n = 34)	Group B (n = 103)	P
Gender, F:M	**31:3**	**87:16**	**0.403**
Age at onset, years	34.9±17.2 (18-71)	36.5±12.5 (18-69)	0.613
Disease duration, months	33.8±25.3 (4-87)	34.3±29.1 (3-108)	0.926
Follow-up, months	29.4±23.2 (4-79)	25.2±22.8 (3-96)	0.355
Relapse number	2.9±3.1 (0-15)	5.0±3.3 (0-17)	0.002
EDSS at initial diagnosis	3.4±1.7	4.1±1.8	0.042
EDSS at last visit	2.4±1.5	3.6±1.8	0.001
NMO-IgG(+), n (%)	23 (67.6)	76 (73.8)	0.309
Spinal cord MRI features			
LETM, n (%)	22 (64.7)	55 (53.4)	0.249
Segments of spinal cord lesions	5.8±4.2	5.3±4.6	0.634
Segments of cervical cord lesions	2.0±2.5	2.9±2.6	0.061
Segments of thoracic cord lesions	3.8±3.4	2.4±3.2	0.030

Abbreviations: NMO = neuromyelitis optica; F = female; M= male; EDSS = Expanded Disability Status Scale; LETM = longitudinally extensive transverse myelitis; Group A = NMO without brain abnormalities; Group B = NMO with brain abnormalities.

Table 2: Clinical, laboratory, and MRI features of the NMO patients with different distribution features of brain abnormalities.

	Group 1 (n = 34)	Group 2 (n = 47)	Group 3 (n = 18)	Group 4 (n = 38)	P	P1	P2	P3	P4	P5	P6
Gender, F:M	31:3	39:8	14:4	34:4	0.471	-	-	-	-	-	-
Age at onset, years	34.9±17.2 (18-71)	37.7±13.1 (18-69)	37.1±11.7 (18-52)	34.7±12.2 (18-64)	0.706	-	-	-	-	-	-
Disease duration, months	33.8±25.3 (4-87)	34.0±34.2 (3-95)	34.3±28.9 (5-108)	34.6±22.5 (4-92)	0.999	-	-	-	-	-	-
Follow-up, months	29.4±23.2 (4-79)	26.6±24.9 (3-96)	24.8±22.7 (2-53)	23.5±20.6 (3-75)	0.744	-	-	-	-	-	-
Relapse number	2.9±3.1 (0-15)	4.2±3.6 (0-17)	5.4±3.0 (2-14)	5.7±2.8 (2-14)	0.002	0.075	0.008	<0.001	0.174	0.033	0.750
EDSS at initial diagnosis	3.4±1.7	3.6±1.5	4.6±2.0	4.6±2.0	0.005	0.673	0.016	0.005	0.028	0.009	0.905
EDSS at last visit	2.4±1.5	3.1±1.5	4.1±1.6	4.0±2.0	<0.001	0.066	0.001	<0.001	0.030	0.015	0.817
NMO-IgG(+), n (%)	23 (67.6)	32 (68.1)	14 (77.8)	30 (78.9)	0.595	-	-	-	-	-	-
Spinal cord MRI features											
LETM, n (%)	22 (64.7)	25 (53.2)	10 (55.6)	20 (52.6)	0.712	-	-	-	-	-	-
Segments of spinal cord lesions	5.8±4.2	5.6±4.9	4.9±4.7	5.3±4.3	0.910	-	-	-	-	-	-
Segments of cervical cord lesions	2.0±2.5	2.9±2.7	2.6±2.9	3.2±2.5	0.246	0.110	0.443	0.056	0.620	0.670	0.421
Segments of thoracic cord lesions	3.8±3.4	2.6±3.6	2.3±3.0	2.1±2.8	0.155	0.118	0.127	0.030	0.736	0.455	0.807

Abbreviations: NMO= neuromyelitis optica; F = female; M= male; EDSS = Expanded Disability Status Scale; LETM = longitudinally extensive transverse myelitis; Group 1 = NMO without brain abnormalities; Group 2 = NMO with only supratentorial lesions; Group 3 = NMO with only brainstem lesions; Group 4 = NMO with both supratentorial and brainstem lesions; P = comparative four groups; P1 = Group 1 vs Group 2; P2 = Group 1 vs Group 3; P3 = Group 1 vs Group 4; P4 = Group 2 vs Group 3; P5 = Group 2 vs Group 4; P6 = Group 3 vs Group 4.

not reach significant difference. The EDSS score at initial diagnosis and EDSS score at last visit of Group 3 were significantly higher than those of Group 2, respectively (p=0.028 and 0.030, respectively). All of the three items, including relapse number, EDSS score at initial diagnosis, and EDSS score at last visit, in Group 4 were significantly higher than those in Group 1 and Group 2, respectively (Group 1 vs Group 4, p<0.001, p=0.005, and p<0.001, respectively; Group 2 vs Group 4, p=0.033, 0.009 and 0.015, respectively). There were no significant differences in the three items above between Group 3 and Group 4, respectively.

No statistical differences were found in NMO-IgG seropositivity among these four groups.

The length of spinal cord MRI lesions of these four groups were similar. There were no significant differences in the length of cervical cord MRI lesions and percentage of patients with LETM among these four groups. The length of cervical cord MRI lesions of Group 4 were longer than those of Group 1, but the difference was not statistically significant. No significant differences were found in the length of thoracic cord MRI lesions among these four groups. However, the length of thoracic cord MRI lesions in Group 1 were significantly longer than those of Group 4 (p=0.030).

Discussion

Brain MRI abnormalities have been reported in previous studies in patients with NMO [6-10,13-15]. However, few studies have focused on effects of brain MRI abnormalities on NMO. In the present study, we found the following features of NMO patients with brain lesions, especially those with brainstem involvement: more frequent relapse and more severe neurologic deficits.

The incidence of brain MRI abnormalities in the patients with NMO was 75.2% (103/137) in our study, which is consistent with other reports on Asian populations [3,16,17]. In the first analysis summarized in Table 1, we have found that the relapse number, EDSS score at initial diagnosis, and EDSS score at last visit were significantly higher in NMO patients with brain abnormalities than those in NMO patients without brain abnormalities. So it seemed that NMO patients with brain abnormalities tend to accompany with more severe neurologic deficits and poor prognosis. However, after the second analysis, we found that these differences were mainly attributed to brainstem involvement. There might be several reasons. First of all, the symptoms and signs of brainstem involve, such as dysphagia, nystagmus, dysarthria, and ataxia, could increase EDSS score. Secondly, combination of brainstem and spinal cord lesions might cause more severe paralysis and sensory disturbance which could also increase EDSS score. Finally, some factors, such as dysphagia and severe paralysis, could increase the risk of infections which might trigger relapse, frequent relapse caused accumulating neurologic deficits which in turn further raised the possibility of infections, forming a vicious cycle. Differing from our study, one research suggested that NMO patients with brainstem lesions had lower annualized relapse rate than those without brainstem lesions, but the EDSS scores were similar [18]. The authors did not explain for these issues. And only 49 NMO patients were enrolled in that study, so we supposed it might be the relative small size of that research that caused the different results. A previous report showed that NMO

spectrum disorder patients with medulla oblongata lesions had a higher annual relapse rate and EDSS score [19], which to some extent, supported our finding.

When comparing patients without brain abnormalities and those with only supratentorial lesions, some items were close to statistical difference. Besides, the relapse number of patients with only brainstem lesions was not significantly higher than that of patients with only supratentorial lesions. But it still seems that supratentorial lesions contribute less than brainstem lesions to the severity and prognosis of patients with NMO. There might be two reasons. On one hand, the number of supratentorial lesions was small and some of supratentorial lesions located in silent areas. On the other hand, most of supratentorial lesions were small, even if they located in functional areas, the clinical symptoms or signs they caused might be covered by those caused by brainstem lesions. It has been reported that NMO patients with extensive brain lesions (EBLs), defined as a large confluent cerebral hemisphere lesions or confluent diencephalic lesions (involving the thalamus and hypothalamus) with diameter ≥30mm on T2-FLAIR or T2WI, had higher diseases activity and worse prognosis [20]. But EBLs are not frequently seen in NMO, especially in the initial stage. In our cohort, there was only four patients with EBLs, so we did not set an individual group for them. And it is unlikely that these four patients would have significant effect on our results. Previous studies have indicated a pathogenic role of NMO-IgG in NMO [21,22]. Some researchers showed that NMO-IgG seropositive patients with NMO had higher relapse number and EDSS score [23-25]. In our study, no difference was found in NMO-IgG seropositivity among different groups, so NMO-IgG seropositivity might not be a cause of different relapse number and EDSS score in NMO patients with different patterns of brain lesions distribution. A study reported that brainstem lesions were more frequently observed in anti-AQP-4 antibody positive than in seronegative patients with NMO, however, the cases number was small [26].

There were no differences either in percentage of patients with LETM or in segments of spinal cord lesions among different groups, so it seemed that the higher relapse number and EDSS score in NMO patients with brain lesions, especially those with brainstem involvement, were not due to more extensive spinal cord damage. Of course, we cannot preclude the possibility that NMO patients with brainstem involvement might develop more extensive spinal cord damage in later stage which might play a role in deterioration of NMO, since they were prone to more frequent relapse. It is out of our expectation that the NMO patients without brain abnormalities had longer thoracic cord lesions than those with both supratentorial and brainstem lesions. And the reason remained unclear. But it should be noted that the NMO patients with both supratentorial and brainstem lesions had a tendency to get longer cervical cord lesions, comparing with those without brain abnormalities. Considering the anatomic sites and functions, it is reasonable to suppose that the effect of thoracic cord lesions might be covered by the cervical cord and brainstem lesions. There are some limitations in this study: (a) the follow-up of some patients is relative short because they are diagnosed recently; (b) bias is inevitable in retrospective studies.

In conclusion, appearance of brain abnormalities in the initial stage, especially brainstem involvement, might be a predictor of severe neurologic deficits and poor prognosis in NMO.

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