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Recovery from optic neuritis attack in neuromyelitis optica spectrum disorder and multiple sclerosis

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ABSTRACT

Background: Both neuromyelitis optica spectrum disorder (NMOsd) and multiple sclerosis (MS) patients experience optic neuritis (ON) attacks characterized by rapidly reduced best-correct visual acuity (BCVA) and slow recovery. Prognosis and effects of recurrence on recovery may differ between disorders but remain unclear.
Objective: To compare ON severity, time and degree of recovery and effects of previous ON between NMOsd and MS patients.
Methods: Retrospective chart review was performed. BCVA measurements acquired before ON, at nadir and during recovery were retrospectively reviewed. Records were obtained on 69 ON attacks in 36 NMOsd patients and 43 attacks in 28 MS patients, including first episodes and recurrences.
Results: NMOsd patients exhibited significantly lower BCVA values at all time points after attack ($P < 0.05$), reached nadir earlier ($P = 0.014$) and regained a smaller fraction of baseline BCVA than MS patients ($P < 0.001$). In NMOsd, relapsed ON resulted in worse recovery and tended to reach nadir earlier than first-episode ON ($P = 0.030$ and 0.059, respectively). In MS, relapsed ON also reached nadir earlier ($P = 0.042$); however, there was no difference in recovery.
Conclusions: Recovery from ON was poorer in NMOsd than in MS and was negatively affected by previous ON attacks.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOsd), including neuromyelitis optica (NMO), is a severe inflammatory disorder of the central nervous system [1]. The defining characteristics of NMOsd are the frequent presence of anti-aquaporin-4 antibodies and lesions predominantly affecting the optic nerves and spinal cord. Multiple sclerosis (MS) is a demyelinating disease of the central nervous system that can also involve the optic nerve. Therefore, both NMOsd and MS can cause optic neuritis (ON).

It was reported that ON is more severe in NMO than in MS [2]. Recently, in MS patients, males and subjects with more severe attacks of ON demonstrated poorer recovery than females and patients with less severe attacks, while young patients exhibited better recovery than older patients [3]. Furthermore, season-adjusted vitamin D level was associated with attack severity but not with recovery. To the best of our knowledge, no factors associated with ON recovery in NMOsd have been identified.

Therefore, we compared the severity and time course of ON as well as the effects of recurrence on outcome between NMOsd and MS patients.

2. Materials and methods

2.1. Subjects

We retrospectively reviewed the records of 75 NMOsd patients, including 48 definite NMO (D-NMO) and 27 partial NMO (P-NMO) and 179 MS patients with a past history of optic neuritis treated at Chiba University Hospital between January 1975 and April 2015 [4,5]. All 75 NMOsd patients fulfilled the 2015 international consensus diagnostic criteria, and all 48 NMO patients fulfilled the diagnostic criteria described by Wingerchuk et al. [1,4]. P-NMO patients were defined as those having anti-aquaporin-4 antibody and either optic neuritis or myelitis according to Mandler's criteria [5]. The MS patients fulfilled the 2010 revisions to the McDonald criteria [6].

In this study, ethics approval was obtained from the ethics committee of Chiba University School of Medicine. All patients provided informed consent.

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2.2. Neuro-ophthalmic evaluations

All patients had ophthalmic examinations, including the measurement of best-corrected visual acuity (BCVA) using a Snellen chart. An ON attack was defined as acute progressive vision loss usually associated with pain on eye movement and documentation of decreased BCVA, visual field defects, relative afferent pupillary defect and compatible findings on fundus examination (normal or transient optic disc oedema with recovery commensurate with BCVA recovery) [2]. Neuro-ophthalmic evaluations were performed by ophthalmologists. We evaluated BCVA before attack and at several time points after attack as available: nadir, 2 weeks (14 ± 3 days), 1 month (30 ± 5 days), 2 months (60 ± 8 days), 3 months (90 ± 10 days) and 6 months (180 ± 12 days). The subjective or objective lowest BCVA in the observational period was defined as nadir. The nadir date was also determined as the last examination date on which a patient realized improvement of visual acuity or the examiner recorded the lowest BCVA. Many of patients were followed up at intervals of once or twice a week until nadir. After nadir, follow-up was performed once a week or two weeks. After a month or two months from an attack, follow-up intervals were extended to once a month or once every two months. Only patients who experienced acute ON, whose BCVA values were lower during the attack and who received at least two neuro-ophthalmic follow-up were included. Patients who showed visual acuity less than finger counting before the attack were excluded. The decimal BCVA was converted to the logarithm of the minimal angle of resolution (logMAR) for statistical analyses, where logMAR = −logBCVA. The difference between logMAR at nadir and logMAR at another time point is expressed as ΔlogMAR (point − nadir).

2.3. Investigations

We retrieved information on sex, disease duration, age at ON onset, anti-aquaporin-4 serostatus and treatment history in the acute phase for ON episodes. LogMAR at each point was compared within and between patient groups. The times from the onset of ON attack to nadir and recovery of baseline BCVA (if present) were compared between NMOsd and MS eyes. The effects of individual treatments were also compared between NMOsd and MS eyes. Differences in recovery between the first ON episode and relapsed ON were compared between NMOsd and MS groups and between D-NMO and P-NMO groups. Finally, correlations between the number of relapses and ΔlogMAR (nadir − point)/ΔlogMAR (nadir − pre) were assessed in NMOsd patients.

2.4. Treatment

Treatments were divided into four categories: 1] intravenous methylprednisolone pulse therapy (1000 mg of methylprednisolone daily for 3 or 5 consecutive days per trial, from one to three trials); 2] intravenous methylprednisolone pulse therapy followed by plasmapheresis (immunoabsorption plasmapheresis performed two times per week, from three to five times in total); 3] low-dose steroid therapy (oral or intravenous steroid therapy at ≤250 mg/day methylprednisolone dose equivalent and tapered to ≤30 mg/day or tapered off, or steroid injection into affected eye at ≤13.2 mg/injection methylprednisolone dose equivalent, from 3 to 20 times in total) and 4] no treatment.

2.5. Statistical analysis

Continuous data were compared between disease groups by Mann–Whitney *U* test and within disease groups by Wilcoxon signed-rank test. Categorical outcomes were evaluated using the chi-square test or Fisher's exact test. Repeated measures analysis of variance (ANOVA) was used to compare disease subgroups, including only those patients receiving follow-up at 3 months. Correlations between the number of relapses and ΔlogMAR (nadir − point)/ΔlogMAR (nadir − pre) were compared using Spearman's rank test. Survival curves were compared using the log-rank test. A P value of <0.05 was considered statistically significant. All statistical tests were conducted using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Demographics, clinical characteristics and treatments for ON in NMOsd and MS patient groups

Demographics and clinical characteristics of ON for all affected eyes are shown in Table 1 and those for all patients (based on the last ON) in Supplementary Table 1. Seventy-six involved eyes in 36 NMOsd patients and 52 involved eyes in 28 MS patients were included (first episodes and relapses). Twenty-one patients with NMOsd and seven patients with MS relapsed more than twice in the observation period. Age at ON onset, positivity for anti-aquaporin-4 antibodies and use of prednisolone pulse plus plasmapheresis treatment for ON attacks were significantly higher in NMOsd patients than in MS patients. The portions of eyes without treatment and patients who received no treatment for ON attacks were significantly higher in the MS group. There were no statistical differences in demographics, clinical characteristics or treatment distribution between D-NMO and P-NMO subgroups. Demographics and clinical characteristics of ON in complete follow-up and incomplete follow-up were also reviewed in both NMOsd and MS eyes respectively (Supplementary Tables 2 and 3). The result showed disease duration in complete follow-up eyes was significantly longer in both NMOsd and MS eyes than in incomplete follow-up eyes (NMOsd; median; 5.0 versus 1.0 years, $P = 0.030$, MS; median; 9.0 versus 2.0 years, $P = 0.040$). The ratio of relapsed ON eyes to first ON eyes and the ratio of eyes treated by intravenous methylprednisolone pulse therapy to eyes treated by other measures were significantly higher in complete follow-up eyes than incomplete follow-up eyes in MS ($P = 0.003$ and 0.014, respectively). Other demographic and baseline BCVA were not different between complete and incomplete follow-up eyes in both NMOsd and MS.

3.2. Differences in the clinical course of optic neuritis between NMOsd and MS patients

Median BCVA values at all times after ON onset were significantly lower (logMAR higher) in NMOsd patients than in MS patients (Fig. 1A), indicating greater severity in NMOsd. Moreover, the final follow-up BCVA value (6 months) did not differ from the baseline (pre ON) in MS patients, indicating full recovery, while the 6 months value in NMOsd patients remained significantly different (logMAR higher than baseline), indicative of incomplete recovery. Analysis restricted to patients receiving BCVA evaluations before ON, at nadir and at 1 month and 3 months post-ON confirmed this significantly poorer course in NMOsd than in MS (Fig. 1B, $P < 0.001$ by repeated measures ANOVA).

3.3. Time from ON attack to nadir and full recovery in NMOsd and MS patients

Times from ON attack to nadir and to regain basement BCVA for each eye in NMOsd and MS patients are shown in Fig. 2A and B, respectively. Kaplan–Meier curves and log-rank tests showed that ON eyes of NMOsd patients reached a nadir significantly earlier than those of MS patients (median; 5.0 versus 8.0 days, $P = 0.014$, Fig. 2A). In addition, ON eyes of NMOsd patients regained baseline BCVA significantly later than those of MS patients (Fig. 2B, $P < 0.001$); half of MS eyes reached baseline BCVA at 67 days, while <40% of NMOsd eyes regained baseline BCVA by the end of the observation period. The median date to regain baseline BCVA in NMOsd eyes was not obtained because <50% of NMOsd eyes regained baseline BCVA by the end of the observation period.