INTRODUCTION

Neuromyelitis optica (NMO), also known as Devic’s syndrome, is an immune-mediated chronic inflammatory disorder of the central nervous system. It is predominantly characterized by attacks of optic neuritis and/or transverse myelitis. In Japan, NMO is considered a clinical variant of multiple sclerosis (MS) and is termed “optic-spinal MS,” although many cases are now identified as NMO. The global diagnostic criteria for NMO were proposed by Wingerchuk et al. in 2006. NMO diagnosis can be made with a history of at least one episode of optic neuritis and one episode of myelitis in conjunction with two of the following three supporting criteria: (1) contiguous spinal cord MRI lesion extending over three or more vertebral segments; (2) brain MRI does not meet the diagnostic criteria for multiple sclerosis; (3) NMO-IgG [anti-aquaporin-4 (AQP4) antibody] seropositive status. However, a definition for NMO spectrum disorders (NMOSD) has been proposed for patients who do not meet these diagnostic criteria. The definition of NMOSD includes isolated longitudinal extensive transverse myelitis (LETM), isolated optic neuritis (ON), and certain types of brainstem encephalitis. There are a few reports on the clinical rehabilitation course of patients with NMOSD attacks. Younger age and two or less attacks were associated with better outcomes in this study.
of NMO patients, although little is known about the recovery process after inflammation and the long-term prognosis. The present study describes 20 patients with NMOSD who received multidisciplinary (MD) inpatient rehabilitation intervention (starting within 2 months after the attack) and evaluates the effectiveness of the treatment.

**METHODS**

**MNOSD Profiles**

A total of 20 consecutive patients with NMOSD who were admitted to Hiroshima City Rehabilitation Hospital over the course of 7 years from April 2008 to March 2014 were evaluated. The use of medical data for research purposes was provided by informed consent on admission. NMOSD diagnoses were confirmed by medical information supplied by previous treatment facilities and were based on the above-mentioned diagnostic criteria, including anti-AQP4 antibody assays.

The patient characteristics on admission are shown in Table 1. The mean patient age was 59.2 years (range, 31–83 years). Four patients were male, and 16 were female (the male:female ratio was 1:4). Anti-AQP4 antibodies were detected in 16 patients. The mean Expanded Disability Status Scale (EDSS) score on admission was 7.1 (range, 3.5–9.0). Two patients were admitted on more than one occasion for recurrent attacks (one patient: two admissions, one patient: three admissions). The coexistence of other diseases was observed: breast cancer with periodic chemotherapy and rehabilitation (one case), depression (two cases), and periodontal disease (one case). One pregnant patient was included in this study. The treatments for acute NMOSD attacks were intravenous methylprednisolone (IVMP) in nine patients, IVMP + plasma exchange in six patients, IVMP + intravenous immunoglobulin (IVIg) in three patients, and IVIg in one patient. One patient received no treatment. Disease-modifying therapy (DMT) was performed in 16 patients (steroids: five patients; immunosuppressive agent: one patient; steroids + immunosuppressive agent: eight patients; steroids + interferon: one patient; steroids + immunosuppressive agent + interferon: one patient). DMT was not performed in four patients. Rehabilitation intervention was started within 14 days after hospitalization. MD inpatient rehabilitation, including physiotherapy, occupational therapy, speech and language therapy, nursing, orthotics, social work, and psychotherapy, was started within 2 months after acute exacerbation. MD rehabilitation care was tailored to suit the specific needs of individual patients.

More than half the patients (11 cases) experienced only an initial NMOSD attack. However, recurrent attacks occurred in other patients (2 in three patients, 3 in one patient, 4 in two patients, 5 in one patient, 7 in one patient, and more than 10 in one patient). The majority of patients (85%) presented with LETM. The lesions were located in both the cervical and thoracic spinal cord regions in 10 patients and in the thoracic spinal cord regions only in 7 patients. Optic neuritis was present in five patients, but only one patient experienced bilateral visual impairment that hindered activities of daily living. Urinary dysfunction (UD) occurred in 14 patients. Pain of myelitic origin was evident in 10 patients; of these, 4 presented with painful tonic seizure (PTS) that interfered with rehabilitation.

**Assessment of Rehabilitation Outcomes**

The NMOSD patients were evaluated for functional status using EDSS. The Frankel classification was used for the myelitis cases. The modified Rankin Scale (mRS) and Functional Independence Measure (FIM) were used as measures of disability. The FIM gain (FIM at discharge – FIM on admission) and FIM efficacy (FIM gain/hospitalization days) were also used. Improvement during inpatient rehabilitation was calculated as the discharge score minus the admission score. The associations between the functional status and the number of days rehabilitation was undertaken, and the total time in rehabilitation, the discharge destination (private residence, acute care hospital, chronic care hospital, or long-term healthcare facility), pain, and urinary dysfunction were analyzed.

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**Table 1. Profiles of 20 NMOSD patients admitted between April 2008 and March 2014**

| Characteristic                        | Value                        |
|--------------------------------------|------------------------------|
| Age (years): mean (range)            | 59.2 (31–83)                 |
| Female, n (%)                        | 16 (80)                      |
| Positive for anti-AQP4 antibody, n (%)| 16 (80)                      |
| Mean EDSS score (range)              | 7.1 (3.5–9.0)                |
| Lesion type, (n)                     | Optic nerve (5), spinal cord (17), brainstem (17) |
| Number of attacks, (n)               | 1 (1), 2 (3), 3 (1), 4 (2), 5 (1), 7 (1), more than 10 (1) |
Statistical Analysis

Statistical analysis was performed using Excel-Toukei version 7.0. Wilcoxon signed-rank tests were used when comparing EDSS, FIM, and mRS scores between the time of admission and discharge. Spearman's rank correlation coefficient and regression analysis were used to estimate functional outcome and the age, number of attack times and hospitalization days. Mann-Whitney U-tests were used to compare functional outcome and urinary dysfunction or pain. Statistical significance was set at P < 0.05.

RESULTS

The average number of hospitalization days for the 20 patients was 97.9, and the average amount of rehabilitation time per day was 152 min. Two patients were transferred to an acute hospital for the treatment for complications (one case of severe heart failure and one case of septic shock caused by acute pyelonephritis) and were subsequently readmitted to our hospital. One pregnant patient was discharged to an acute care hospital as a result of NMO relapse. Finally, 16 patients (72.7%) were discharged to private residences, and 3 patients were transferred to chronic hospital care [2 of these 3 patients had high EDSS scores (9.0) at discharge].

The analysis results for 19 patients are shown in Table 2 (the pregnant patient discharged to acute hospital care was not included in the final analysis). The average EDSS score at discharge (5.9) represented an improvement compared with that on admission (7.1), although the difference was not statistically significant. The mean change in EDSS score (i.e., the EDSS score on admission minus that at discharge) was −1.2. The EDSS score on admission was strongly correlated with FIM on admission (P = 0.001). Similarly, the EDSS score at discharge was strongly correlated with FIM at discharge (P = 0.001). The FIM score was significantly improved from 81.4 to 101.7 during hospitalization (P < 0.05). The average FIM gain was 20.3 and the FIM efficacy was 0.2/day. However, although the motor FIM score significantly improved (P < 0.01), there was no change in the cognitive FIM score. The mRS score changed from 3.7 to 3.1 during hospitalization. With regard to the Frankel grade, although the residual functional level remained unaltered, five patients had an improved grade from C to D.

There was no significant correlation between age and EDSS score on admission. Similarly, the FIM score on admission was not significantly related to age. Age did have a significant correlation with the improvement in EDSS score during rehabilitation (P < 0.05). However, there was no significant correlation between FIM gain and age. There was a tendency toward recovery in younger patients. The change in EDSS scores showed no correlation with hospitalization days, although FIM gain was significantly correlated with hospitalization days (P < 0.01). EDSS scores tend to be improved so that there is little attack number of time, but statistical significance was not found (P = 0.05). The changes in EDSS scores varied in patients with only a first attack, although a ≥ 1.5 EDSS score change was seen in the case with less than two attacks (Fig. 1).

Patients with UD had higher EDSS scores on admission compared with patients without UD (7.8 with UD vs. 5.0 without UD, P < 0.01). FIM scores on admission were lower in patients with UD (72.0 with UD vs. 107.8 without UD, P < 0.01), whereas FIM scores on discharge showed no significant difference. FIM gain was significantly higher in patients with UD compared with patients without UD (P < 0.05), and the number of hospitalization days was significantly greater in patients with UD compared with patients without UD (119.1 days with UD vs. 61.6 without UD, P < 0.01) (Table 3). Patients with PTS tended to have high EDSS scores on admission compared with patients without PTS, although there was no statistically significant difference (8.3 with PTS vs. 6.8 without PTS). Rehabilitation outcomes did not differ

| Table 2. Results of the analyses of 19 patients |
|-----------------------------------------------|
| On admission | At discharge | P  |
|----------------|-------------|----|
| EDSS 7.1   | 5.9         | n.s.|
| EDSS change | −1.2          |    |
| FIM 81.4   | 101.7       | < 0.05|
| FIM gain   | 20.3         |    |
| Motor FIM 49.7 | 69.3       | < 0.01|
| Cognitive FIM 31.7 | 32.4       | n.s.|
| mRS 3.7    | 3.1         | n.s.|

The data are mean values.
between patients with and without PTS.

DISCUSSION

The present study evaluated the effects of rehabilitation in 20 patients with NMOSD. The following generalizations can be made: (1) ON and LETM were common features; (2) many patients exhibited severe disabilities, even from the initial attack; (3) as a DMT, corticosteroids and/or immunosuppressive agents were administered to the majority of patients. In our study, 5 patients (25%) had ON and 17 patients (85%) had myelitis. Only one patient exhibited bilateral visual impairment; this patient had a high EDSS score because of myelitis. Therefore, in our experience, the main aim of inpatient rehabilitation for NMOSD patients was to improve the spinal cord lesion-related disabilities. Patients with UD and PTS as a result of spinal cord lesions had high EDSS scores on admission. In particular, patients with UD required a long period of inpatient rehabilitation. The urinary management plan and guidance for intermittent self-catheterization were likely causes for the prolonged duration of hospitalization.

Myelitis in NMOSD patients appears as longitudinal cord lesions that often extend from the cervical to the thoracic level. As a result, the severity of disability in NMOSD patients is high, even from the initial attack. Although the follow-up periods in this study were less than 5 months, EDSS and FIM were useful for the evaluation of MD rehabilitation in NMOSD patients. Average EDSS scores improved from 7.1 to 5.9 following inpatient rehabilitation intervention. The average FIM gain was 20.3 and the FIM efficacy was 0.2/day, suggesting that adequate rehabilitation can improve the mobilization capacity and reduce limitations on activity for NMOSD patients, irrespective of disease severity. Younger age and having two or less attacks were factors for greater rehabilitation efficacy.

Previous studies have shown that NMOSD is a distinct disorder from MS, according to detection of NMO-IgG (anti-AQP4 antibody) and immunopathological findings of NMO lesions. Necrotic degeneration of astrocytes, i.e., astrocytopathy, caused by anti-AQP4 antibodies is the principal pathogenesis of NMO. Astrocytopathy is followed by oligodendrocyte demyelination in the optic nerve and spinal cord. Clinically, optic neuritis and myelitis are characteristics of NMO. The former affects the optic chiasma, and both affect the optic nerves, resulting in a high risk for blindness. Spinal cord lesions extending over three or more vertebral segments and with central gray matter involvement are striking features of optic myelitis. Some NMOSD patients present with brain lesions involving the medulla oblongata and diencephalon, which is consistent with the location of AQP4 expression. On rare occasions, broad white matter and tumefactive lesions have also been reported.

Overall, 34% of NMOSD patients show permanent motor dysfunction as a sequel, and 23% of them become wheel-

Table 3. Comparison of patients with/without urinary dysfunction (UD)

|                      | With UD (n = 14) | Without UD (n = 5) | P    |
|----------------------|-----------------|--------------------|------|
| EDSS on admission    | 7.8             | 5.0                | < 0.01|
| EDSS at discharge    | 6.6             | 3.9                | < 0.05|
| EDSS change          | 1.2             | 1.1                | n.s. |
| FIM on admission     | 72.0            | 107.8              | < 0.01|
| FIM at discharge     | 95.9            | 118.2              | n.s. |
| FIM gain             | 23.9            | 10.4               | < 0.05|
| Hospitalization days | 119.1           | 61.6               | < 0.01|

The data are mean values.
A cohort study of MS patients revealed that the median disease duration characterized by cane and wheelchair use are 17 years and 24 years, respectively. Therefore, the disease duration for gait disturbance characteristics to develop in NMOSD patients seems to be shorter than that in MS patients. A number of randomized and controlled clinical trials have shown that rehabilitation for MS patients is effective for functional recovery, maintenance of activity, and gains in quality of life. However, to date, only two case reports and one retrospective study of MD rehabilitation covering 15 inpatients with NMO have been published. No randomized controlled clinical trials have been carried out to assess NMOSD rehabilitation.

The administration of corticosteroids and/or immunosuppressive agents is recommended to prevent relapse in anti-AQP4-positive NMOSD patients. The same is recommended also for anti-AQP4-negative NMOSD patients with severe first attack and incomplete recovery. In the present study, 16 of 20 patients received DMT. Additionally, the rehabilitation included particular care for infection prevention and early detection of side effects. One patient receiving corticosteroids developed acute pyelonephritis that resulted in septic shock during hospitalization. This case revealed the need for close observation to detect neurogenic bladder and to manage the risk of urinary tract infection, especially in patients undergoing DMT. Our results suggested that adequate DMT is necessary to produce the desired rehabilitation effects.

Intensive inpatient rehabilitation intervention for NMOSD patients improves function and reduces disability even in patients with high-severity disease. MD rehabilitation is particularly important for improved mobilization and the management of urinary dysfunction. Rehabilitation should include educational training for intermittent self-catheterization and drug adjustments for NMOSD. Further research involving controlled trials may be necessary to confirm the therapeutic efficacy of rehabilitation for NMO patients.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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