Effectiveness of multi-disciplinary rehabilitation for patients with Neuromyelitis Optica

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Introduction: Neuromyelitis optica (NMO), previously considered a subtype of multiple sclerosis (MS), is now known to be a unique disorder associated with autoantibodies against aquaporin-4. The rehabilitation protocols for MS have been applied to NMO, without specific measures of efficacy.

Purpose: The evaluation of the effectiveness of an MS type inpatient rehabilitation program for patients with NMO.

Patient and Methods: Retrospective chart reviews of 15 inpatients with NMO and 32 inpatients with MS. Clinical severity was assessed by the Expanded Disability Status Scale (EDSS), functional assessments were scored using the Functional Independence Measure (FIM), the Montebello Rehabilitation Factor Score (MRFS), and the Functional Ambulation Category (FAC). There was a higher percentage of women in the NMO group (87% vs 56% $P = 0.003$). The MS group had significantly more cognitive and communication deficits ($P = 0.003$ and $P = 0.00001$). No significant differences were found in admission FIM, EDSS and FAC scores.

Results: Both groups benefitted, however at discharge, the NMO group showed greater improvement in FIM scores (NMO admission 79 ± 24 , discharge 98 ± 21 ; MS admission 80 ± 28 , discharge 89 ± 28); and lower EDSS score (NMO from 7.2 ± 1.4 to 6.3 ± 1.4 ; MS from 7.4 ± 1.4 to 7 ± 1.5).

Conclusions: Inpatient multidisciplinary rehabilitation programs available for the patients with MS may be successfully implemented for patients with NMO.

Keywords: Neuromyelitis optica, Multiple sclerosis, Rehabilitation, Functional outcomes, Body structure and functions, Expanded Disability Status Scale

Introduction

Neuromyelitis optica (NMO, Devic) is a demyelinating disease, characterized by myelitis and optic neuritis.¹ This disease can be monophasic or relapsing-remitting. NMO was suspected to be part of the spectrum of multiple sclerosis (MS), until NMO-IgG, a specific antibody, was discovered in 2004, and new diagnostic criteria were published. These include the finding of 2 definite criteria (optic neuritis (ON) and acute myelitis) and at least two of three supportive criteria (contiguous spinal cord MRI lesion extending over 3 vertebral segments; brain MRI not meeting diagnostic criteria for multiple sclerosis; and seropositive NMO-IgG).²

NMO is an uncommon disorder in Western populations. In a study that was conducted among a population of 3 million over 10 years in North West England there was a minimum estimated incidence of 0.4/million/year and a prevalence of 4/million, representing one out of 200 patients with demyelinating disease.³ Another study found that these patients represent less than 1% of the patients with demyelinating disease.⁴ The average age of onset is 39 and the disease affects women 3–6 times more than men.^{3–7} In a recent study of 60 patients, the median survival was found to be 8 years, with a range of 1–30 years.⁶ Another study, conducted on patients with the relapsing form, found a mortality rate of 25% after 11 years of disease duration.⁷

The discovery of specific antibodies, NMO-IgG, directed against the water channel antigen aquaporin

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4, the most abundant water channel in the CNS, established NMO as a unique antibody mediated disease.⁸ The exact involvement of NMO-IgG in the immunopathogenetic cascade of the disease is still not clear and T cell reaction has also been reported in patients with NMO.⁹ The NMO-IgG has 76% sensitivity and 94% specificity for clinically definite NMO. However, even with the most sensitive assays, 10–25% of patients clinically diagnosed with NMO are seronegative for NMO-IgG. There are differences in the clinical course between seropositive and seronegative patients with NMO. Seropositive patients were found to be predominantly female and to experience more severe clinical attacks including severe visual and motor symptoms. On the other hand, bilateral ON at onset was more common in seronegatives, as was simultaneous ON and myelitis.¹⁰ Moreover, the time to diagnosis of NMO was shorter and the course of disease was more often monophasic in seronegative patients. No difference was found regarding age at onset, time to relapse, annualized relapse rates, outcome from relapse (complete, partial, no recovery), annualized EDSS increase, mortality rate, or other clinical and laboratory findings between patients with seropositive and seronegative NMO.

Impairments, like blindness and paraplegia or tetraplegia, appear early in NMO when compared to MS.^{3,4,11} Within 5 years of disease onset, over 50% of the patients with relapsing NMO, have monocular blindness or cannot ambulate without assistance⁴ compared to the patients with MS, who take an average of 28 years to need assistance in ambulation.¹²

To our knowledge, the only publications available on the effectiveness of rehabilitation treatment of patients with NMO are case reports by Schreiber *et al.* and Goyal *et al.*^{13,14} A possible explanation to the lack of research is the rarity of the disease and the lack of clear cut diagnostic criteria until recently. Considered for many years as a MS-like disease, the rehabilitation protocols for MS have been applied to those with NMO. However, the spinal cord symptoms such as para or tetraparesis and sphincters' disturbances and the visual symptoms tend to be more severe than in those with MS.¹⁵

Several studies have evaluated the effects of interdisciplinary rehabilitation programs and specific exercise programs in patients with MS.^{16–18} Strong evidence was found in favor of exercise therapy compared with no exercise therapy in terms of muscle power, function, exercise tolerance functions and mobility-related activities. Physical therapy has been shown to be effective in improving gait and mobility, and reducing the risk of falls of patients with MS.¹⁷ The clinical characteristics and disease course in NMO requires adaptation of

existing rehabilitation programs, and effectiveness needs to be determined.

The aim of our study is to evaluate the efficacy of an MS type inpatient rehabilitation program adapted for individuals with NMO by comparing outcomes to those of individuals with MS.

Methods

Population

This is a retrospective review of computerized charts of NMO inpatients, hospitalized between 1/2007 and 12/2010, in two rehabilitation centers in Israel. Individuals with MS treated in the same rehabilitation units during the same time period served as a control group. Patients with MS and with NMO were respectively diagnosed according to the 2010 McDonald criteria and the NMO diagnostic criteria.^{3,19} All of the patients with MS were admitted to the acute hospital due to relapse. Patients with NMO included those admitted to the acute hospital due to relapse, and others for diagnostic work-up. Both patients with MS and those with NMO were treated with IV steroids while they were inpatients in the neurology departments. The treatment was discontinued prior to the rehabilitation admission. In those patients receiving disease modifying agents such as Cytoxan, IVIG or interferon, the treatment was continued during rehabilitation.

Data were recorded for each patient including demographics (sex, age at admission to the department, marital status and employment) and time from the first episode of the disease to the admission to rehabilitation, as well as the clinical and rehabilitation parameters and outcomes.

Interdisciplinary rehabilitation program

Both populations had completed a structured interdisciplinary rehabilitation program with specific goals according to the limitations of body functions and structures, as well as the barriers encountered in their basic and expanded activities. The program included physiatrist and rehabilitation nursing assessments, physiotherapy, occupational therapy, hydrotherapy, social work and rehabilitation psychology assessments, and neuro-optometric evaluation for those with visual impairments. The therapy programs were scheduled for five days per week with three to five hours of treatment time per day. Most required neuro-urological evaluation and management. While those with NMO were most likely to require the neuro-optometric evaluation and treatment program, those with MS were more likely to undergo comprehensive neuro-psychological and cognitive testing.

The discharge criteria include lack of progress towards rehabilitation goals, and inability to achieve the goals on an outpatient basis.

Neurological and functional assessments

The severity of the neurological impairments was assessed by components of body structure and function of the ICF classification²⁰: communication (expressed as speech or language disorders), swallowing, bladder and bowel control, skin integrity, cognitive function, and limb weakness (para/tetra/hemi; plegia/paresis). The impairment severity of patients with NMO and with MS was assessed by the Expanded Disability Status Scale (EDSS)²¹ at admission and discharge from the rehabilitation departments. The functional assessment was done using the Functional Independence Measure (FIM),²² the Montebello Rehabilitation Factor Score (MRFS), and the Functional Ambulation Category (FAC).²³ The differences between the scores at admission and discharge, as well as the length of stay (LOS) in rehabilitation represented the rehabilitation outcomes. The MRFS was used to overcome the ceiling effect of the FIM.²⁴ Scores were thus measured in relation to the patient's specific potential for improvement and reflected the relative functional gain as follow: MRFS efficacy was defined as Discharge FIM-Admission FIM/Maximum Possible FIM-Admission FIM, and MRFS efficiency was defined as MRFS Efficacy Score/LOS.

EDSS was performed by the admitting physician and approved by the attending physician.

The FIM scoring was done by the 'FIM team' (PT, OT, nurse) in specific sessions, independent of treatment. The team was trained in-house by an FIM certified rehabilitation nurse. Although members of the FIM team are involved in direct patient care, they constitute a small percentage of the staff.

Statistical analysis

Comparisons of admission and discharge data for each group were done by two-tailed independent *t* test (*P* = 0.05). Differences between the NMO and MS groups

were also analyzed by two-tailed independent *t* test. *F* test was administrated to evaluate variances equality in each comparison (*P* = 0.05). Statistical Package for Social Sciences (SPSS) 13 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

Results

Demographic and clinical characteristics

There were 15 patients in the NMO group and 32 patients in the MS group with mean age of 40.8 ± 15.7 and 47.9 ± 11.4 years, respectively (*P* = 0.13; Table 1). 13 (87%) of the patients with NMO were women as opposed to only 18 (56%) in the MS group (*P* = 0.003). No statistical difference was found in any of the other parameters including marital status, employment etc. The age at disease onset was similar in the two groups, however patients with NMO were referred to rehabilitation earlier in the course of the disease (3.8 ± 4.03 vs 14.8 ± 11.85 years, *P* = 0.001). In the NMO group, the course of the disease was monophasic in five, and relapsing in the remaining ten. Eleven of the fifteen were positive for Aquaporin 4 antibodies. Five were treated with corticosteroids, 3 with azathioprine, 2 with cyclophosphamide and 4 by a combination of corticosteroids, IVIG and azathioprine. In the MS group, the course of the disease was relapsing-remitting in fourteen patients, secondary progressive in thirteen and primary progressive in five. Thirteen patients were not receiving maintenance treatment, 11 were being treated with interferon therapy, 3 with copaxone, 2 with chemotherapy agents and 3 with corticosteroids. The LOS was significantly longer in the NMO group (mean 68.2 ± 55 days vs 38.3 ± 27.9 days, *P* = 0.012).

Body structure and function impairments

The body structure and functions parameters are presented in Table 2. Both groups had similar impairment rates in bladder and bowel functions, skin integrity, swallowing, and limb weakness. None of the NMO group had communications problems compared to fourteen patients with MS and only one patient with NMO

Table 1 Demographics and clinical characteristics

Characteristics	NMO group <i>N</i> = 15, <i>n</i> (%)	MS group <i>N</i> = 32, <i>n</i> (%)	<i>P</i> -value
Age	40.8 ± 15.7	47.9 ± 11.4	0.13
Sex (female)	13 (87)	18 (56)	0.003
Marital status	11 (73)	17 (53.1)	0.25
Employment	2 (13.3)	6 (19)	0.64
Age of disease diagnosis, (years)	38.1 ± 14.7	32.9 ± 12.2	0.47
Time from diagnosis to admission to rehabilitation, (years)	3.8 ± 4.03	14.8 ± 11.85	0.001

NMO = Neuromyelitis Optica, MS = Multiple sclerosis.

Table 2 Body structure and body functions impairments

Body structure and function		NMO group N = 15, n (%)	MS group N = 32, n (%)	P-value
Limbs weakness	Tetraparesis	7 (46.7)	18 (56)	0.55
	Paraparesis	7 (46.7)	12 (38)	
	Hemiparesis	1 (6.7)	2 (6)	
Bladder and bowel function		14 (93.3)	29 (90.6)	0.63
Skin		1 (6.7)	3 (9.4)	0.63
Swallowing		0 (0)	6 (18.8)	0.007
Communication		0 (0)	13 (40.7)	0.003
Cognition		1 (6.7)	24 (75)	0.00001

NMO = Neuromyelitis Optica, MS = Multiple Sclerosis.

with cognitive impairments, compared to 24 in the MS group.

Activity limitations

There was no significant difference between the groups for the EDSS, FIM and FAC scores on admission to rehabilitation. Both groups made significant improvements in their EDSS scores (Fig. 1); in the NMO group from 7.2 ± 1.4 to 6.3 ± 1.4 ($P = 0.0003$) and in the MS group from 7.4 ± 1.4 to 7 ± 1.5 ($P = 0.007$). The discharge EDSS score was significantly lower in the NMO group ($P = 0.05$). The patients with NMO also had significantly greater improvement in functions expressed by the FIM scores at discharge. (NMO admission 79 ± 24 , discharge 98 ± 21 ($P = 0.0008$); MS admission 80 ± 28 , discharge 89 ± 28 ($P = 0.2$; Fig. 2). The efficacy and the efficiency of the rehabilitation process of the patients with NMO were higher without reaching a statistically significant difference. The MRFS efficacy in the NMO group was 0.4 ± 0.2 , vs. 0.2 ± 0.3 in the MS group ($P = 0.064$), and the MRFS

efficiency was 0.011 ± 0.015 in the NMO group vs. 0.008 ± 0.01 in the MS group ($P = 0.309$). There was a significant improvement in walking capacity within each group, (Fig. 3), from 1.3 ± 1.8 to 2.8 ± 1.6 ($P = 0.002$) in the NMO group and from 1.3 ± 1.7 to 2.2 ± 1.9 ($P = 0.0005$) in the MS group, without statistical difference between the groups. There were no differences in rehabilitation outcomes found between patients with seropositive and seronegative NMO, or between those presenting with a monophasic or relapsing course.

Discussion

To the best of our knowledge, this is the first study comparing the characteristics and rehabilitation achievements of an NMO population to patients with MS treated in multidisciplinary inpatient rehabilitation programs. Two previous studies described rehabilitation outcomes of patients with NMO.^{13,14} Schreiber *et al.*, described 3 patients with blindness and complete

Figure 1 Expanded Disability Status Scale (EDSS) scores at admission and at discharge of Neuromyelitis Optica (NMO) and Multiple sclerosis (MS) groups. EDSS scores improved significantly during the rehabilitation period in both groups MS (a: $P = 0.007$), NMO (b: $P = 0.0003$), with no intergroup differences: Admission (c: $P = 0.19$); Discharge (d: $P = 0.05$). (Significance = $P < 0.05$).

Figure 2 Functional Independence Measure (FIM) scores at admission and at discharge of Neuromyelitis Optica (NMO) and Multiple sclerosis (MS) groups. Significant improvement in the FIM scores in the NMO group (b: $P = 0.0008$), but not in the MS group (a: $P = 0.2$). There were no significant differences between the groups in their respective FIM scores on admission (c: $P = 0.93$) or at discharge (d: $P = 0.31$). (Significance = $P < 0.05$).

Figure 3 Functional Ambulation Category (FAC) scores at admission and discharge of Neuromyelitis Optica (NMO) and Multiple sclerosis (MS) groups . Both groups showed significant improvement in walking capacity as expressed by the FAC scores MS (a: $P = 0.0005$), NMO (b: $P = 0.002$). No statistical difference between the groups: Admission (c: $P = 0.99$), Discharge (d: $P = 0.30$). (Significance = $P < 0.05$)

paraplegia due to relapsing NMO, who were treated in an inpatient rehabilitation unit for 1 to 1.5 months.¹³ All of the patients improved, but none reached functional ambulation, and all needed assistance in daily living at discharge. Despite being at a lower functional level on admission and discharge than our patients, the FIM score gains were similar to our group. There was no information regarding the medical treatment of the NMO in these patients. In another case report, a 55-year-old woman with bilateral optic neuritis and recurrent myelitis, regained the ability to walk with a tripod cane and improved in ADL abilities while under treatment with corticosteroids and azathioprine during her rehabilitation.¹⁴ The length of stay was not given.

In our study, the rehabilitation programs were identical to those that have been described as effective for MS.^{25,26} The two groups were comparable in age, marital status and employment at admission to rehabilitation. Surprisingly there were more males than females in the MS group, possibly due to the earlier onset in patients of primary and secondary progressive MS among this group.^{27,28} The patients with NMO were admitted to the rehabilitation program at an average of 3.8 years from the initial diagnosis compared to almost 15 years in the MS group. This finding reflects the difference in the course and severity of symptoms of the diseases. The frequency and severity of inflammatory relapses are usually greater in NMO than in MS.²⁹ This likely leads to earlier referral of patients with NMO for rehabilitation. By contrast, patients with MS typically have milder attacks with good recovery; permanent disability generally occurs later during the secondary progressive phase of the disease.³⁰

Our results indicated that both the NMO and MS groups benefitted from the rehabilitation program, yet the NMO group obtained greater functional achievements as expressed by the FIM scores. The longer LOS for NMO group is probably a reflection of the rapid deterioration of functional abilities and early loss of independence. The slower onset and peaks of deterioration due to exacerbations in MS gives the opportunity to gradually accommodate to the changes in function, including environmental adaptations, obtaining appropriate equipment, and patient/family/caregiver education. Even though the duration of rehabilitation treatment was longer for the patients with NMO, the FIM efficacy and efficiency were higher. We hypothesize that the generally intact cognitive and the communication status was the reason for the better rehabilitation outcomes.

We suggest that the close follow up of neurological status and adjustments and fine tuning of medical treatments during a relatively prolonged rehabilitation LOS contributed to the gains made by our patients with NMO. We reported previously of a patient who did not improve during the initial phase of rehabilitation, but improved significantly and gained independence in ambulation after a change in her medical treatment.³¹ Theoretically if patients with NMO are treated with an effective preventive therapy and a strong immune suppression during the acute attack, the chance of a better rehabilitation is higher due to less progression in the months following the relapse.

We are aware of a number of limitations in our study. It was a retrospective study, and not all of the data were readily available from the unaffiliated acute care centers. In particular, we did not always have MRI scans that may have allowed for correlating the anatomic lesions with the functional status, and all of the information regarding the disease modifying treatments.

Conclusion

The patients with NMO showed improvements during inpatient rehabilitation comparable to patients with MS, including neurological (EDSS) and functional (FIM and walking) gains. These results suggest that the existing inpatient multidisciplinary rehabilitation programs available for the patients with MS should be implemented for patients with NMO, with appropriate adjustments according to the patients' needs.

Disclaimer statements

Contributors YN: collecting the data, interpreting the data, writing the article in whole, and revising the article. EM: collecting the data, interpreting the data,

writing the article in part, and revising the article. HW: interpreting the data, writing the article in whole, and revising the article. AB: analysing the data, interpreting the data, and revising the article. UG: collecting the data, interpreting the data, and revising the article. AVD: collecting the data, interpreting the data, and revising the article. IS: collecting the data, interpreting the data, and revising the article. ZM: conceiving and designing the study, interpreting the data, writing the article in whole, and revising the article. GZ: conceiving and designing the study, obtaining ethics approval, interpreting the data, writing the article in whole, and revising the article.

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