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A population-based and cross-sectional study of the long-term prognosis in multifocal motor neuropathy

Long-term outcome in multifocal motor neuropathy

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No supplementary data provided
Abstract

Objective: To evaluate the long-term outcome in Danish patients treated for multifocal motor neuropathy (MMN).

Methods: A population-based, cross-sectional study of patients referred to the Danish hospital system between 1985 and 2006.

Results: Thirty-four MMN patients were identified, three had died of unrelated diseases, 10 were excluded, one did not reply to study request and 20 were included. The median disease duration was 24 years (IQR: 18.5 – 31.0). Compared to 24 healthy matched control subjects, the Rasch-built Overall Disability Scale for Multifocal Motor Neuropathy was reduced by 9%, the Neuropathy Impairment Score showed a threefold increase, the isokinetic strength was reduced by 29%, the grip strength by 56%, the Timed 25-Foot Walk was prolonged by 13% and the EQ-5D-5L-Index value was impaired by 20%. The isokinetic strength was significantly more impaired at the wrist and ankle as compared to the elbow and knee, and one patient had lost ambulation due to instability at the ankle. Patients were considerably more fatigued and had substantially impaired hand dexterity, while mood, aerobic capacity, social adjustment and working capacity were not affected.

Regression analysis showed that lag-time until start of initial therapy lead to impaired long-term outcome without any effect of disease duration.

Conclusion: Long-term prognosis in treated MMN is characterized by moderate to severe impairment primarily affecting dexterity and stability at the ankle. Our observations support previous observations that the long-term impairment in MMN might be improved following earlier start of therapy and that an effect of disease duration cannot be demonstrated.
**Glossary:** 9-HPT = Nine-Hole Peg Test; MMN = Multifocal Motor Neuropathy; FSS = Fatigue Severity Scale; IKS = Isokinetic Strength; MMN-RODS = Rasch-built Overall Disability Scale for Multifocal Motor Neuropathy; MDI = Major Depression Inventory; NIS = Neuropathy Impairment Score; SAS-SR = Social Adjustment Scale – Self Report: Short; SSST = Six Spot Step Test; T25FW = Timed 25-Foot Walk
Introduction

Since the first description of MMN in the late 1980’s six long-term studies that included patients treated with either IVIG or a combination of IVIG and cyclophosphamide have been published (Azulay et al., 1997; Van den Berg-Vos et al., 2002; Terenghi et al., 2004; Vucic et al., 2004; Van Asseldonk et al., 2006; Cats et al., 2010). In these studies, the number of patients ranged from 10 to 88. The total disease duration at the last evaluation varied from 8 to 18 years, the treatment duration period being 5-11 years (Azulay et al., 1997; Van den Berg-Vos et al., 2002; Terenghi et al., 2004; Vucic et al., 2004; Cats et al., 2010). Two of the studies have used a consecutive follow-up design (Azulay et al., 1997; Cats et al., 2010), but none of the studies included control subjects.

We conducted a population-based, cross-sectional study of the long-term outcome in Danish patients treated for MMN. In order to study patients with long disease duration, only patients with a first contact to a neurologist before 2007 were included.
Materials and Methods

The study is cross sectional and population based with a search period from January 2^{nd}, 2016 to February 28^{th}, 2018. All patients in Denmark fulfilling the EFNS/PNS criteria for MMN and treated with immune modulating therapy during the period Jan 1^{st}, 1985 – Dec 31^{st}, 2006 were eligible. The study period was from January 2^{nd}, 2018 to August 30^{th}, 2018. Exclusion criteria were concomitant disabling neurological or orthopedic disorders, diabetes mellitus, other neuropathies, chemotherapy and age above 90 years. A blood sample was taken for exclusion of diabetes, B12 and folic acid deficiency, kidney disease and HIV infection.

To evaluate the scores of disability, neuropathy impairment, function and quality of life a group of 24 healthy subjects matched with respect to age, gender, weight and height was included using the same exclusion criteria as for the MMN patients.

Register search

The diagnostic codes DG61.8 (other inflammatory polyneuropathies) and DG61.9 (inflammatory neuropathy, unspecified) as well as the Danish procedure code BOHJ10 (treatment with high-dose immunoglobulin) were searched in the Danish National Patient Register, in which information regarding diagnosis and treatment has been registered since 1970 for all contacts to the Danish healthcare system. This search was combined with a search through local registers at the university hospitals in Aarhus, Odense and Copenhagen. According to the Specialty Plan of The
National Board of Health in Denmark these three hospitals have the privilege to treat all Danish MMN patients.

To evaluate the significance of MMN for mortality, deceased patients were identified in the Danish Register of Causes of Death.

The search through registers was conducted between January 2\textsuperscript{nd}, 2016 and February 28\textsuperscript{th}, 2018.

**Patient examination**

Patient records were reviewed by AA to find eligible MMN patients and to record disease details regarding onset, course, treatment, and lag-time from symptom onset until initiation of immunoglobulin therapy. All patients and control subjects were interviewed and examined by the same physician (AA), either at the Neuromuscular Laboratory, Department of Neurology, Aarhus University Hospital or at the Neuromuscular Out-patient Clinic, Copenhagen University Hospital, Rigshospitalet.

The Local Ethics Committee of the Capital Region (record no. H-16038590) and The Danish Data Protection Agency (record nr.: 2012-58-0004) approved the protocol. All MMN patients and control subjects gave written informed consent.

**Evaluation of the primary end-points**
Disability was scored using a self-reporting questionnaire, the Rasch-built Overall Disability Scale for Multifocal Motor Neuropathy (MMN-RODS), evaluating limitations of physical activity and social participation at scores ranging from 0 (most severe disability) to 50 (no disability) (Vanhoutte et al., 2015).

Neurological impairment was rated using the Neuropathy Impairment Score (NIS, 0: no impairment, 220: maximum impairment) assessing 21 pairs of muscle groups, five pairs of deep tendon reflexes, and four sensory modalities, as described elsewhere (Dyck et al., 1997).

Mean isokinetic strength (IKS) at the elbow, wrist, knee and ankle was evaluated either at the weakest side or in case of equal strength at a random side using dynamometry (Biodex System Pro 4/3®; Biodex Medical Systems Inc., Shirley, NY, USA) (Harbo et al., 2012). Normalized strength was expressed as a ratio between the measured and predicted value of each muscle group, the latter being obtained from data of 178 healthy subjects (Harbo et al., 2008, 2012).

Using a hand-held dynamometer (Jamar®; Sammons Preston Roylan, Chicago, IL, USA), grip strength was measured 3 times at each side, the mean of the maximum values at each side being used for evaluation (Mathiowetz et al., 1985).

The Timed 25-Foot Walk (T25FW) was applied for evaluation of walking (Rudick et al., 1997) and for dexterity a Nine-Hole Peg Test (9-HPT) (Goodkin et al., 1988).

The EQ-5D-5L-Index Value scale (EuroQol Group, 1990; van Hout et al., 2012) was utilized to evaluate quality of life.
Evaluation of secondary end-points

For evaluation of combined weakness and ataxia, a Six Spot Step Test (SSST) in which 5 blocks are kicked away during walking was applied (Nieuwenhuis et al., 2006; Kreuzfeldt et al., 2017).

For mood, social performance, self-rated quality of life and severity of fatigue, we used the Major Depression Inventory (MDI) (Bech, 1997), the 24-item Social Adjustment Scale – Self Report: Short (SAS-SR) (Gameroff et al., 2012), the EQ-5D-5L-VAS (EuroQol Group, 1990; van Hout et al., 2012) and the Fatigue Severity Scale (FSS) (Krupp et al., 1989) as described elsewhere.

Aerobic capacity was evaluated by means of a 6 min submaximal cycle test (Astrand et al., 2003). The obtained heart rate was transformed to aerobic capacity using an Åstrand-Ryhming nomogram, a previously published formula and age correction following regression analysis (Astrand and Ryhming, 1954; Astrand, 1960).

Statistical analysis

After a Bonferroni correction, the six primary end-points were tested using a two-sided level of significance of 0.0083. The remaining end-points were tested with a 0.05 two-sided level of significance. Due to the number of observations, data are presented as medians and interquartile ranges (IQR), the Mann-Whitney U test being applied for group comparisons. Dichotomous data were compared using Fisher’s exact test. For regression analysis either non-transformed or
logarithmic data were applied using best fit. Sample size calculation for the control subjects was performed applying the primary parameter with the lowest expected significant difference, namely the EQ-5D-5L-Index value. Based on the values obtained in 51 patients with chronic inflammatory demyelinating neuropathy and 20 healthy control subjects (personal communication), a difference of 15% was expected to be of clinical significance with a standard deviation of 15% for patients and 10% for control subjects. For a significance level of 0.0083, a power of 0.8, an expected inclusion of at least 19 MMN patients, 22 control subjects were needed. To accommodate for the use of the slightly weaker non-parametric tests, 24 control subjects were included. For calculation of statistics the SAS software package was applied.

Data availability statement

Anonymized participant data, study protocol and statistical analysis plan can be shared following contact to the corresponding author.

Results

National patient identification

The flowchart for patient identification in the Danish National Patient Register and in the registers of the three hospitals responsible for diagnosis and treatment of MMN is shown in Fig. 1. A total of 2,128 patients were identified. In 487 deceased patients the record was not accessible, but their death certificates neither registered G61.8 as a potential cause of death nor as an active disease
at the time of death. In 347 alive patients no case records could be identified, but no registrations of a present or previous diagnosis of MMN could be identified in the electrophysiological records. A detailed review of the remaining 1,294 case records identified 34 MMN patients, of whom 3 had died from unrelated diseases, 10 were excluded according to the study criteria, one did not reply to study request and 20 accepted participation and were included in the study. The 31 alive MMN patients with a first hospital contact before 2006 combined with 21 patients with a first contact after 2006 gives a point prevalence of 52 recognized and treated MMN patients in Denmark.

**Characteristics of MMN patients and control subjects**

Characteristics of the 20 MMN patients and 24 control subjects are shown in Table 1. Patients and controls did not differ with respect to age, weight, height and gender. The median duration of MMN was 24 years (IRQ: 19 – 31), the median time since first contact to a neurologist being 21 years (IQR: 17 – 29). MMN related symptoms were present for a median of 7 years (IQR: 3 – 12) before treatment was started, the treatment duration period being 14 years (IQR: 10 – 20). All but one patient were ambulatory with independent walking function.

**Primary end-point data**

Values for the primary end-point variables are shown in Table 2. The disability score, MMN-RODS, was reduced by 9% as compared to the control subjects. The NIS was moderately affected being 31 a.u. in patients as compared to 11 a.u. in controls. Median IKS was reduced by
29% in patients as compared to controls. The strength at the wrist and ankle was severely to moderately affected with a reduction of 38% and 24%, respectively. In comparison the strength at the elbow and knee was moderately to mildly reduced by 20% and 11%, respectively, the difference between the proximal strength at the elbow and knee versus the distal strength at the wrist and ankle being significant (p = 0.01).

The grip strength was severely impaired in patients being reduced by 56% as compared to controls. The T25FW was mildly prolonged by 13% and the EQ-5D-5L-Index value impaired by 20%.

Regression coefficients following univariate regression analysis of the MMN-RODS and the NIS against the remaining primary and secondary end-points are presented in Table 3. The NIS was related to primary end-points including the IKS, grip strength, quality of life (Fig. 2), whereas the MMN-RODS neither was related to the NIS nor any of the other primary end-points, except for being correlated to the quality of life following Spearman Rank Correlation test.

Secondary end-points

Results for the secondary end-points are shown in Table 4. The MMN patients were more fatigued according to the FSS questionnaire and performed the 9-HPT and SSST slower than the controls. Moreover, the self-rated quality of life, the EQ-5D-5L-VAS score was reduced by 14%. The aerobic capacity, mood (MDI), social performance (SAS-SR-Short) and the amount of weekly paid work did not differ between the patients and the control subjects. The regression coefficients
showed that the NIS was related to 9HPT, SSST and the self-rated quality of life, whereas the MMN-RODS was related to dexterity, mood and the self-rated quality of life. Corrected for age, the lag-time from symptom onset until treatment initiation was associated to both the NIS and the IKS. Doubling of the lag time results in a NIS increase of 4.9 a.u. (95% 1.0 – 8.8, p = 0.02) (Fig. 3). The lag time was neither associated nor correlated to the MMN-RODS (p = 0.2, p = 0.3, respectively).
Discussion

We performed a cross-sectional, population-based study on 20 treated Danish MMN patients with a median disease duration of 24 years, the longest observation period hitherto reported. In the present study the disease duration period was 24 years as compared to 8-18 years in previous studies, the treatment period being 14 years in our study as compared to 5-11 years (Azulay et al., 1997; Van den Berg-Vos et al., 2002; Terenghi et al., 2004; Vucic et al., 2004; Cats et al., 2010). The obtained results were compared to those of 24 matched control subjects, making it possible to evaluate the degree of impairment. Patients had a moderate to severe degree of long-term neurological impairment primarily affecting the distal musculature with severe impairment of hand and finger movements. Also, quality of life was mildly reduced with an increased degree of fatigue, but social performances were preserved. The impairment including muscular weakness was related to lag-time from start of symptoms to start of therapy. In the present study MMN patients were moderately to severely impaired despite the majority received effective IVIG treatment. The median MRC was decreased by 8% in an outcome study of 88 patients (Cats et al., 2010), while the mean MRC scores were reduced by 18% in a clinical and electrophysiological study of 20 patients (Van Asseldonk et al., 2006), by 6% in a case record review of 10 patients (Vucic et al., 2004), by 15% in a 8.2 year follow-up of 10 patients (Terenghi et al., 2004) and by 6% in a clinical and electrophysiological follow-up study of 11 patients (Van den Berg-Vos et al., 2002). Even though a direct comparison between the continuous variables used in our study and the ordinal variables used in previous studies is not possible, our observations seem to be in accordance with these other findings.
The Danish National Patient Register contains diagnostic and treatment codes for every patient contact encountered in the national health care system since 1970. Based on the unique social security number for every citizen in Denmark, all patients can be identified according to codes for diagnosis and treatment. If a correct diagnostic or treatment code is registered once, it will appear in the search. To accommodate the risk that a patient during the entire disease course never received a correct code, local registers at the three university hospitals treating MMN were searched as well. None of the patients registered with the relevant study codes but without clinical records had any files in the associated electrophysiological departments. Since MMN patients usually have a protracted course stretching over many years it is unlikely that any of these patients lacking older clinical records had MMN.

We found significant deteriorations of all primary end-points. The NIS was moderately impaired in patients compared to the values of the control subjects. The difference between the groups is primarily attributed to distal weakness and impaired deep tendon reflexes. The NIS values obtained in the present study are higher than those obtained in 51 long-term treated CIDP subjects (personal communication). Following univariate regression analysis, the NIS was associated to the IKS, grip strength, both quality of life scores, SSST and the 9-HPT.

The IKS was 29% weaker in the MMN patients than in control subjects. Since MMN is highly asymmetric and strength has been evaluated at the most affected side, our IKS value represents the manifestations of the disorder rather than the overall muscle performance. In the present study, the strength at the wrist and ankle were significantly more impaired than at the elbow and knee. This is in line with earlier observations, showing that MMN affects the strength more
severely at distal than at proximal joints (Cats et al., 2010). Moreover, attention should be drawn to the fact that the ankle plantar flexion was reduced by 23% in our MMN patients. Moderate impairment of the ankle plantar flexion is not easily appreciated in clinical settings and might affect walking and especially the running function.

The primary end-point that was the least impaired in the patients was the MMN-RODS. Moreover, the dispersion of the scores obtained in patients was low, the IQR being 5.5 at a 50-grade scale. In addition, following univariate regression analysis the MMN-RODS raw score was only associated to three end-point values, namely the self-rated quality of life, mood and dexterity, while it was further associated to the examiner-rated quality of life and fatigue following non-parametric correlation analysis. It is possible that analysis using the nomogram for the Rasch transformation would strengthen the relationship between RODS and the various end points.

The most impaired primary variable was the grip strength. This is in contrast to the relative preservation of finger flexion strength observed in the present study and previously reported (Cats et al., 2010). The explanation could be that flexion of fingers using a handheld dynamometer requires the application of extensional force at the wrist to counteract the secondary flexional force provided by the finger flexors.

All but one MMN patients were ambulatory without walking aids, but the T25FW and the SSST were both moderately impaired. The non-ambulatory patient could stand up and walk with assistance from two persons, only. The lack of ambulation was attributed to complete paralysis of both flexion and extension at the ankles, preventing stabilization of the feet. This patient was treated with azathioprine and had never received immunoglobulin treatment.
The MMN patients were significantly more fatigued than the control subjects. This is in line with earlier observations in MMN (Cats et al., 2010) and in inflammatory neuropathies (Merkies et al., 1999). In general, it is recommended that fatigue should be assessed as part of the clinical evaluation in inflammatory neuropathy (Merkies et al., 1999; Vanhoutte et al., 2013). However, we were not able to demonstrate a relationship between fatigue and neurological impairment (NIS). Previous reports have shown that the degree of impairment and disability is associated with axonal loss and not with features of demyelination (Van Asseldonk et al., 2006; Cats et al., 2010). It is, therefore, possible that fatigue might be a feature of the current level of inflammation rather than of the disease burden.

As for the primary end-points, the most impaired secondary end-point (9-HPT) affected the hand function. This is in line with previous reports stating that MMN primarily affects distal parts of the limbs, especially the hand (Cats et al., 2010).

The aerobic capacity, mood, social adjustment and amount of work did not differ between MMN patients and the controls. Both the objectively assessed and self-rated quality of life scores were, however, moderately affected in MMN patients compared to the control subjects. In addition, the MMN-RODS, which reflects home activities, was slightly but significantly impaired. These finding are in contrast to the moderate to severe impairments observed using other scales indicating that MMN patients are capable of maintaining a relatively normal life despite considerable impairment and function deficits.

In accordance with previous reports, the lag-time from disease onset until initiation of IVIG treatment was positively associated with neurological impairment evaluated by the NIS and...
IKS for patients of the same age (Van Asseldonk et al., 2006; Cats et al., 2010). Moreover, in both these studies, the significant association persisted following regression against the duration of treatment. In the present study neither age nor duration of treatment had any significant association to NIS or IKS impairment following inclusion of lag-time until treatment initiation. In fact, the coefficient of determination, \( R^2 \), for the multivariate regression analysis of lag-time before treatment initiation and age against the IKS was 0.61, with p-values for the regression coefficients of the lag-time and age being 0.002 and 0.3 respectively. Thus, most of the long-term variation of IKS for patients with the same age is explained by the lag-time before treatment initiation. Part of the impairment obtained in previous studies on MMN might well be explained by the long lag-time of several years before start of therapy (Azulay et al., 1997; Van den Berg-Vos et al., 2002; Terenghi et al., 2004; Vucic et al., 2004; Van Asseldonk et al., 2006; Cats et al., 2010). This explanation is supported by two previous reports (Van Asseldonk et al., 2006; Cats et al., 2010) as well as by the present study. All in all, the latency before treatment initiation seems to be an established prognostic factor for the long-term condition in patients with MMN.

Previous reports have described a decrease of muscle strength during IVIG-treatment (Van den Berg-Vos et al., 2002; Terenghi et al., 2004). Although one of the studies reported an increase in administered IVIG dose throughout the follow-up period (Cats et al., 2010), two studies reported no effect of duration of treatment (Van Asseldonk et al., 2006; Cats et al., 2010). This is further supported by a clinical and electrophysiological follow-up study of more than 7 years, in which no clinical or electrophysiological deterioration took place throughout the treatment period (Vucic et al., 2004).
As previously described, the latency until treatment initiation is predictive for the long-term outcome. Consequently, the application of the disease burden data in two subsets of patients with short and long latency would demonstrate a difference. The median latency until IVIG initiation in our patients was 7.0 y (2.5 y – 11.5 y). Post hoc analysis dividing the patients into two groups showed that the median NIS in the short latency group with a latency of less than 7 years was 20 a.u. (IQR: 12 au. – 24 a.u.) compared to 36 a.u. (IQR: 28 a.u. – 51 a.u.) in the long latency group (p = 0.03). This difference could not be demonstrated for RODS-MMN.

Two of our patients had not received IVIG treatment for three years due to apparent disease inactivity. Moreover, two patients had at least once resumed regular treatment due to slowly deterioration after IVIG discontinuation. Two previous studies using systematic and consecutive inclusion of patients have reported that a few patients could discontinue IVIG therapy following partial remission (Azulay et al., 1997; Cats et al., 2010). However, in all previous reports, the fraction of patients in sustained remission is small. Moreover, the indolent nature of MMN makes it difficult to appreciate a minor progression in patients apparently being in remission. Thus, it remains questionable to what degree MMN patients go into remission, if at all.

We have performed a cross-sectional study of MMN patients with the longest disease duration hitherto reported and compared the obtained values with those of control subjects. Our study shows that long-term patients with MMN have a moderate to severe degree of impairment and that the early initiation of IVIG treatment, hopefully, might reduce the disease burden.
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Disclosures

This study is funded with a PhD study grant from Baxter/Baxalta, now part of Shire

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### Table 1. Demographics and clinical data in 20 patients with MMN and in 24 controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (Interquartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of MMN (y)</td>
<td>24.0 (18.5 – 31.0)</td>
</tr>
<tr>
<td>Time since first contact to neurologist (y)</td>
<td>21.0 (16.5 – 29.0)</td>
</tr>
<tr>
<td>Disease duration until IVIG initiation (y)</td>
<td>7.0 (2.5 – 11.5)</td>
</tr>
<tr>
<td>Age at onset (y)</td>
<td>35.5 (31.5 – 38.5)</td>
</tr>
<tr>
<td>Current treatment</td>
<td></td>
</tr>
<tr>
<td>IVIG:SCIG (n)</td>
<td>8:9</td>
</tr>
<tr>
<td>Time interval between IVIG infusions</td>
<td>5.0 (3.5 – 7.0)</td>
</tr>
<tr>
<td>IgG dose (g/kg bodyweight/month)</td>
<td>1.41 (1.35 – 1.77)</td>
</tr>
<tr>
<td>Azathioprine (n)</td>
<td>1</td>
</tr>
<tr>
<td>No treatment</td>
<td>2</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>59.5 (51.5 – 66.5)</td>
</tr>
<tr>
<td>Controls</td>
<td>61.5 (52.5 – 67.5)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>79.5 (69.5 – 90.0)</td>
</tr>
<tr>
<td>Controls</td>
<td>76.5 (63.5 – 84.0)</td>
</tr>
<tr>
<td>Height (m)</td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>1.78 (1.69 – 1.85)</td>
</tr>
<tr>
<td>Controls</td>
<td>1.76 (1.68 – 1.80)</td>
</tr>
<tr>
<td>Sex, M:F (n)</td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>13:7</td>
</tr>
<tr>
<td>Controls</td>
<td>14:10</td>
</tr>
</tbody>
</table>

### Table 2. Median and interquartile range for the 6 primary end-points in 20 MMN patients and 24 controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>MMN</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIS (a.u.; 0 – 220)</td>
<td>30.6 (16.5 – 41.8)§§</td>
<td>11.0 (4.5 – 16.5)</td>
</tr>
<tr>
<td>MMN-RODS raw score (a.u.; 0 – 50)</td>
<td>45.5 (42.0 – 47.5)§§</td>
<td>50.0 (50.0 – 50.0)</td>
</tr>
<tr>
<td>IKS Overall Percentage (0 – 100)</td>
<td>59.8 (54.5 – 74.0)§§</td>
<td>84.7 (78.6 – 88.7)</td>
</tr>
<tr>
<td>Grip strength (kilograms force)</td>
<td>14.5 (11.0 – 26.5)§</td>
<td>33.3 (24.5 – 46.0)</td>
</tr>
<tr>
<td>T25FW (seconds)</td>
<td>4.3 (3.9 – 5.2)§</td>
<td>3.8 (3.3 – 4.0)</td>
</tr>
<tr>
<td>EQ-5D-5L-Index value (0 – 1)</td>
<td>0.80 (0.74 – 0.87)§</td>
<td>1.00 (0.86 – 1.00)</td>
</tr>
</tbody>
</table>

p-values for group comparisons:

- § p < 0.01
- §§ p < 0.0001
Table 3. Regression coefficients following univariate regression analysis of the NIS against all primary and secondary end-points

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Effect of a 1 a.u. increase of MMN-RODS</th>
<th>Effect of a 1 a.u. increase of NIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMN-RODS</td>
<td>20</td>
<td>1</td>
<td>-0.2 (-0.5 – 0.05)</td>
</tr>
<tr>
<td>NIS</td>
<td></td>
<td>-0.7 (-1.5 – 0.2)</td>
<td>1</td>
</tr>
<tr>
<td>IKS</td>
<td>20</td>
<td>0.5 (-0.3 – 1.3)</td>
<td>-0.8 (-1.1 – -0.6)§§§</td>
</tr>
<tr>
<td>Grip Strength</td>
<td>20</td>
<td>0.4 (-0.1 – 1.0)</td>
<td>-0.5 (-0.7 – -0.3)§§§</td>
</tr>
<tr>
<td>T25FW</td>
<td>19</td>
<td>-0.005 (-0.1 – 0.1)</td>
<td>0.04 (-0.008 – 0.09)</td>
</tr>
<tr>
<td>EQ-5D-5L-Index value</td>
<td>20</td>
<td>NA*</td>
<td>-0.004 (-0.007 – -0.0006)$</td>
</tr>
<tr>
<td>FSS</td>
<td>20</td>
<td>NA*</td>
<td>0.02 (-0.02 – 0.06)</td>
</tr>
<tr>
<td>SSST</td>
<td>19</td>
<td>-0.0003 (-0.2 – 0.2)</td>
<td>1.2% (0.1% – 2.2%)§§</td>
</tr>
<tr>
<td>EQ-5D-5L-VAS score</td>
<td>20</td>
<td>1.1 (0.5 – 1.7)§§</td>
<td>-0.6 (-1.0 – -0.3)§§§</td>
</tr>
<tr>
<td>MDI</td>
<td>20</td>
<td>-0.2 (-0.4 – -0.04)$</td>
<td>0.07 (-0.03 – 0.2)</td>
</tr>
<tr>
<td>SAS-SR-Short</td>
<td>20</td>
<td>0.06 (-0.2 – 0.3)</td>
<td>-0.01 (-0.1 – 0.1)</td>
</tr>
<tr>
<td>VO$_2$</td>
<td>16</td>
<td>0.5 (-0.4 – 1.4)</td>
<td>0.05 (-0.5 – 0.6)</td>
</tr>
<tr>
<td>9-HPT</td>
<td>20</td>
<td>-3.2% (-6.0% – -0.4%)§§</td>
<td>3.2% (2.1% – 4.2%)§§§</td>
</tr>
</tbody>
</table>

* Spearman rank correlation: EQ-5D-5L-Index value: Rho = 0.7, p = 0.0008, FSS: Rho = -0.5, p = 0.04.

§ p < 0.05
§§ p < 0.01
§§§ p < 0.0001

Table 4. Median and interquartile range for the 8 secondary end-points in 20 MMN patients and 24 controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>MMN</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSS (1 – 7)</td>
<td>3.4 (2.6 – 5.4)$§§</td>
<td>2.3 (1.7 – 3.0)</td>
</tr>
<tr>
<td>VO2 max (mL/kg/min)*</td>
<td>27.8 (24.3 – 37.2)</td>
<td>37.6 (29.0 – 43.4)</td>
</tr>
<tr>
<td>SSST (seconds)</td>
<td>5.8 (4.9 – 7.7)$§</td>
<td>4.9 (4.6 – 5.4)</td>
</tr>
<tr>
<td>9-HPT (seconds)</td>
<td>29.8 (22.4 – 59.0)$§§</td>
<td>19.7 (19.0 – 21.6)</td>
</tr>
<tr>
<td>EQ-5D-5L VAS score (0 – 100)</td>
<td>77.5 (67.5 – 85.0)$§§</td>
<td>90.0 (82.5 – 96.5)</td>
</tr>
<tr>
<td>MDI (0 – 50)</td>
<td>5.0 (3.0 – 7.5)</td>
<td>3.0 (2.0 – 5.0)</td>
</tr>
<tr>
<td>SAS-SR-Short (35 – 90)</td>
<td>43.0 (41.0 – 45.5)</td>
<td>43.5 (41.5 – 47.0)</td>
</tr>
<tr>
<td>Weekly hours of paid work**</td>
<td>37.0 (8.0 – 37.0)</td>
<td>34.5 (9.0 – 37.0)</td>
</tr>
</tbody>
</table>
Median (interquartile range)
*Results from 16 patients and 23 controls.
**Data of 14 patients and 16 controls under 65 years of age
§ p < 0.05
§§ p < 0.01
**Figure titles and legends:**

Title:

Figure 1. Flowchart for the inclusion of patients

Title:

Figure 2. Univariate regression analysis of the NIS against four of the primary and secondary endpoints with 95% confidence interval (grey shading) and prediction limits (area between dashed lines).

Title:

Figure 3. Regression of latency until treatment onset against the NIS corrected for age.
Search lists: 2,128

Not fulfilling inclusion criteria: 2,094
- 1st contact after 2006: 12
- MMN not confirmed: 2,082
  - Possible MMN: 7

Included: 34

Deceased: 3
- MMN: 0
- Cancer: 1
- Cardiac disease: 1
- Unknown/not registered: 1

Excluded: 10 (mean age: 67.6 years)
- Radiation therapy: 1
- Dementia: 1
- Diabetes: 5
- Disabling orthopedic disease: 1
- Other: 2

No study request reply: 1 (age: 87 years)

Participating MMN patients: 20 (mean age: 59.8 years)