A population-based study of long-term outcome in treated chronic inflammatory demyelinating polyneuropathy

Al-Zuhairy, Ali; Sindrup, Søren H.; Andersen, Henning; Jakobsen, Johannes

Published in:
Muscle and Nerve

DOI:
10.1002/mus.26772

Publication date:
2020

Document version:
Accepted manuscript

Citation for published version (APA):

Go to publication entry in University of Southern Denmark's Research Portal

Terms of use
This work is brought to you by the University of Southern Denmark. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

• You may download this work for personal use only.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk
A Population-Based Study of Long-Term Outcome in Treated CIDP

Long-term outcome in CIDP

Ali Al-Zuhairy (MD)1, Søren H. Sindrup (DMSc)2, Henning Andersen (DMSc)3, Johannes Jakobsen (DMSc)1
1Department of Neurology, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark
2Department of Neurology, Odense University Hospital, Odense, Denmark
3Department of Neurology, Aarhus University Hospital, Aarhus, Denmark

Corresponding author:
Ali Al-Zuhairy, MD
Department of Neurology
Rigshospitalet
Copenhagen University Hospital
Blegdamsvej 9
DK-2100 Copenhagen
Denmark
E-mail: al_zuhairy@hotmail.com
Office: +45 35 45 61 35

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

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

Disclosure of Conflicts of Interest
Henning Andersen has received research and travel support from Octapharma, CSL Behring and Genzyme/Sanofi, speaker honoraria from Genzyme/Sanofi and Pfizer, and served as consultant on advisory board of UCB Pharma. Johannes Jakobsen has received a research grant from Baxter/Baxalta, now part of Takeda, to cover the budget for a PhD study without providing any personal benefits. The remaining authors have no conflicts of interest.
A Population-Based Study of Long-Term Outcome in Treated Chronic Inflammatory Demyelinating Polyneuropathy

Abstract

Introduction: The effect of long-lasting immune-modulating therapy was studied in patients with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).

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

Results: The 51 participating patients had a median disease duration of 16 years (inter quartile range: 14 – 21). Twenty-seven (53%) had discontinued therapy and 46 walked independently. Disability and isokinetic strength were impaired by 17% and 20%, respectively, as compared to matched control subjects. For a few patients long-term CIDP was associated with severe morbidity (6%) and even mortality (1%). Prolongation of time until start of therapy was associated with an increased burden of long-term disability.

Discussion: Long-term prognosis in treated CIDP is characterized by limited disability in the majority of patients. Disability is related to delay of therapy. Therefore, more attention should be given to early treatment start in CIDP.

Keywords: CIDP, Chronic inflammatory demyelinating polyneuropathy, prognosis, outcome, disability
Introduction

Patients with chronic inflammatory demyelinating polyneuropathy (CIDP) can be treated with immune modulating therapy, including immunoglobulins, plasma exchange and steroids. The therapeutic short-term effect has been demonstrated in trials with a maximum duration of 1-2 years. The long-term outcome of immune modulating treatment has been evaluated in hospital based follow-up series or cross sectional studies. During the period 1975 to 2006 seven major hospital-based studies on patients with a CIDP mean duration of 4.4 to 10.6 years were published. In the first reported series from 1975 the mean disease duration was 7.5 years in 53 consecutively referred patients with progression or without remission. Thirty-eight patients had been treated with steroids, 60% were ambulatory, 28% were bedridden or confined to a wheelchair of whom 6 (10%) had died from their disease. In the six subsequent hospital-based series, and in a recent case-record review, the number of patients ranged from 38 to 92, the duration of CIDP from 3.9 to 10.6 years, the relative number of patients who were non-ambulatory from 2 to 13% and the number of patients who had died from their disease from 2 to 11%.

Immune modulating treatment for CIDP has been available for three to four decades. Therefore, it is possible to conduct studies with a longer disease duration than previously. In addition, the easier access to such therapy during recent years might well have improved the long-term outcome.

For these reasons we conducted a study of treated Danish CIDP patients with a disease duration of more than 10 years.
Materials and Methods

To obtain an estimate of the long-term prognosis after introduction of effective immune-modulating therapy the inclusion of newly diagnosed patients was limited to the period from 1985 to 2006. All identified patients in Denmark meeting the EFNS/PNS criteria for probable or definite CIDP treated with immune modulating therapy during the period Jan 1st, 1985 – Dec 31st, 2006 were eligible. Exclusion criteria were concomitant disabling neurological or orthopedic disorders, diabetes mellitus, other neuropathies, chemotherapy and age above 90 years. At the follow-up evaluation a blood sample was taken for exclusion of diabetes, B12 and folic acid deficiency, kidney disease and HIV infection.

To evaluate patient performance, a group of 20 matched control subjects was included using the same exclusion criteria as for the CIDP patients. Following advertisement potential control subjects had a telephone interview providing information on age, weight, height, gender and health.

Register search

Patients were recruited from the total population of Denmark (5.25 million by Jan 1st, 1996) through the Danish National Patient Register using the diagnostic codes DG61.8 (other inflammatory polyneuropathies) and DG61.9 (inflammatory neuropathy, unspecified) effective after January 1st, 1994. Also, patients were searched for with the Danish procedure code BOHJ10
Long-term outcome in CIDP

(treatment with high-dose immunoglobulin) effective after January 1\textsuperscript{st}, 1999. Data for the three requested codes were delivered from the National Board of Health as electronic files.

According to the Specialty Plan of The National Board of Health in Denmark CIDP is treated at the university hospitals in Aarhus, Odense and Copenhagen, only. To ensure inclusion of patients, who during the entire period neither had been registered with the correct diagnostic code nor had received immunoglobulin therapy nor only had contact to the healthcare system prior to 1994, local registers at the three university hospitals were thoroughly searched including electrophysiology databases. In order to evaluate the significance of CIDP for the causes of death, deceased patients were identified in the Danish Register of Cause of Death.

The search through registers was conducted during the period January 2\textsuperscript{nd}, 2016 to February 28\textsuperscript{th}, 2018 and eligible patients were included during December 5\textsuperscript{th}, 2016 to March 2\textsuperscript{nd}, 2018.

Subject examination

Patient records were reviewed by AA in order to identify eligible CIDP patients and to record details about severity, duration, course and treatment of disease. Patients and spouses were informed about initial case report information at the time of start of symptoms. In case of new information this was included in the estimate for duration of symptoms. Since patients with a GBS-like onset of CIDP could have a different course and treatment response, information was recorded as to whether the disease start was acute with development of symptoms within a few weeks.\textsuperscript{13,14} All patients and control subjects were interviewed and examined by the same author (AA), either at
the Neuromuscular Laboratory, Department of Neurology, Aarhus University Hospital or at the
Neuromuscular Out-patient Clinic, Copenhagen University Hospital, Rigshospitalet. Self-reporting
questionnaires were completed by the study participants. Subsequently, the various test procedures
were carried out in a laboratory setting, the duration of the whole procedure being three hours.

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

Evaluation of impairment, function and disability

Disability was evaluated with the Rasch-built Overall Disability Scale (R-ODS) for
immune-mediated peripheral neuropathies (I-RODS) which is a self-reporting questionnaire
evaluating limitations of physical activity and social participation with scores ranging from 0 (most
severe disability) to 100 (no disability) following translation of the raw sum score to a centile
metric value.\textsuperscript{15}

Neurological impairment was evaluated using the Neuropathy Impairment Score
(NIS).\textsuperscript{16} Grading of muscle strength of 21 pairs of muscle groups are scored as follows: Normal
strength = 0; 75% of normal strength = 1; 50% = 2; 25% = 3; paralyzed = 4; five pairs of deep
tendon reflexes and four modalities of sensation at the index finger and hallux at both sides are
scored from 0 (normal) to 2 (absent), resulting in a total maximum impairment score of 220.
Dynamometry (Biodex System Pro 4/3®; Biodex Medical Systems Inc., Shirley, NY, USA) was applied for evaluation of isokinetic strength (IKS) at elbow, wrist, knee and ankle on the weakest side of the patient. In case of equal strength the side selection was made at random as in the controls. To weight all muscle groups equally, normalized strength was expressed as a ratio between the measured and predicted value, the latter being obtained from data of 178 healthy subjects reported from our laboratory.4,17

Grip Strength was measured 3 times on each side with a hand-held dynamometer (Jamar®; Sammons Preston Rolyan, Chicago, IL, USA), the mean of the maximum values at each side being the modified parameter applied.18

For evaluation of walking a Timed 25-Foot Walk (T25FW)19 and for dexterity a Nine-Hole Peg Test (9-HPT)20 were applied. For evaluation of combined weakness and ataxia, a Six Spot Step Test (SSST) in which 5 blocks are kicked away during walking was included.21,22

Aerobic capacity was measured during a 6 minute submaximal exercise test using a cycle ergometer.23 The obtained heart rate at the given effect was transformed to aerobic capacity using an Åstrand-Ryhming nomogram, including a previously published formula with age correction obtained at regression analysis.24,25

Evaluation of fatigue, pain, mood, quality of life and social adjustment

A Fatigue Severity Scale (FSS)26 was applied including nine questions with answers ranging from 1 (no fatigue) to 7 (maximum fatigue) using the average value as the index score.
Pain was graded according to an 11-point Pain-Intensity Numerical Rating Scale (PI-NRS) and expressed as the mean value of the worst, least and current pain intensity within the last 24 hours, mean values ranging between 0 (no pain) and 10 (most severe pain).27

Quality of life was evaluated using an EQ-5D-5L-VAS and an Index Value scale.28,29 Mood was graded with a Major Depression Inventory (MDI) scale30 and social performance with a 24-item Social Adjustment Scale – Self Report: Short (SAS-SR).31

**Statistical analysis**

The study defined six primary end-points, namely scores for I-RODS, NIS, IKS, grip strength, T25FW and EQ-5D-5L-Index value. Following a Bonferroni correction, a two-sided level of significance of 0.0083 was applied. All other end-points were defined secondary and tested using a 0.05 two-sided level of significance. Gaussian data, whether transformed or not, are presented as means and 95% confidence intervals (CI), differences being tested using Student’s unpaired $t$ test. Inspection of residuals according to model assumptions was performed. Non-Gaussian distributed data are presented as medians and inter quartile ranges (IQR), a Mann Whitney $U$ test being used for comparisons. Descriptive data in Table 1 are presented as medians and IQR. McNemar’s test was applied to assess for changes of binary paired data. For regression analysis either non-transformed or logarithmic data were applied using best fit. Sample size calculation for the control subjects, was performed on the primary parameter with the lowest expected significant difference, namely the EQ-5D-5L-Index value. A difference of 15% was expected to be of clinical significance with a standard deviation of 15%. For a significance level of 0.0083, a power of 0.8 and an expected
inclusion of at least 45 CIDP patients, 18 control subjects were needed. For calculation of statistics the SAS software package was applied.

Results

National Patient Identification

Fig. 1 shows the flowchart for patient identification in the National Patient Register and in registers of the three hospitals responsible for diagnosis and treatment of CIDP.

After cross-checking several lists, a total of 2,128 patients were identified, of whom 487 had died resulting in closure of the case records. The records of the deceased patients were no longer 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 clinical case records could be identified. However, no registration of peripheral neuropathy appeared, neither in the local registers nor in the electrophysiological case records. After detailed review of the remaining 1294 case records, 129 patients meeting entry criteria were identified.

Twenty-three patients with CIDP had died. In one case the death was due to respiratory insufficiency secondary to CIDP. The other fatalities were due to cancer in 10 cases, cardiovascular diseases in 5 cases and other disorders in 7 cases. The mean age at death was 71.1 y (95% CI: 66.7 – 75.5; data of 22 patients) and the mean time since death was 9.0 y (95% CI: 6.8 – 11.2; data of 22 patients). Among the 106 living CIDP patients 39 were excluded according to study criteria, 12 declined to participate and 4 did not reply to the request for study participation. There
was no difference between participating and non-participating eligible patients with respect to age, disease duration, time since first neurological contact, duration of treatment or gender (p-values 0.09, 0.4, 0.9, 0.3, and 0.1, respectively). The type of onset differed, however, the percentage of acute, GBS-like onset being higher among non-participants than participants (50% vs. 14%, p = 0.02).

**Characteristics of CIDP Patients and Control Subjects**

Table 1 shows characteristics for the 51 CIDP patients and 20 control subjects. There were no differences between patients and controls with respect to age, sex, weight or height. The median duration of therapy was 13.0 y (IQR: 11.0 – 16.5) for patients still treated and 6.3 y (IQR: 3.0 – 9.0, p < 0.0001) for patients no longer treated.

A comparison of CIDP patients still receiving immune-modulating therapy versus patients no longer treated showed that the latency before treatment onset was significantly prolonged in still treated patients (3.0 y, IQR: 0.5 – 5.5) compared to patients no longer treated (0.5 y, IQR: 0.15 – 1, p = 0.0004). Still treated patients were significantly more disabled (I-RODS = 65, IQR: 56.5 – 77.5) and impaired (NIS = 27.8, IQR: 21.5 – 47.4; IKS = 64.3, IQR: 52.5 – 78.2) than those no longer treated the I-RODS, NIS and IKS being 100.0 (IQR: 83.0 – 100.0, p < 0.0001), 19.0 (IQR: 9.5 – 26.5, p = 0.003) and 79.8 (IQR: 71.7 – 86.5, p = 0.005) respectively. In addition, the patients still treated had a lower quality of life score than those no longer treated (p = 0.001).
**Primary End-point Data**

Table 2 shows the values for the six primary end-points in CIDP patients and controls. According to five of the six primary end-point parameters the patients were moderately impaired compared to control subjects.

Mean isokinetic strength (IKS) was reduced by 20% in CIDP patients compared to controls. At the elbow the mean reduction was 18%, at the wrist 16%, at the knee 19% and at the ankle 30%. The mean strength of the foot dorsal and plantar flexors compared to controls was significantly more reduced than the combined mean strength of the other six muscle groups (p = 0.003).

Grip strength did not differ significantly between patients and control subjects.

The regression coefficients between the I-RODS score and the NIS versus the remaining primary and secondary end-point values are shown in a supplementary Table. Fig. 2 shows the relationships between the I-RODS score and four of the primary end-points, namely the NIS, the IKS, the grip strength and quality of life (EQ-5D-5L-Index value), the coefficient of determination ($R^2$) ranging from 0.4 to 0.7 indicating a close association.

Multivariate regression analysis showed that lag-time until treatment was related to the I-RODS score and the IKS. The regression coefficient of lag-time against the I-RODS for patients of the same age was -2.5 a.u. (95% CI -4.3 – -0.7, p = 0.007) (Fig. 3).

**Secondary End-points**
The results for the secondary end-points in CIDP patients and in control subjects are shown in Table 3.

**Discussion**

In the previous studies on long-term outcome in CIDP design, diagnostic criteria, therapy and length of observation periods varies.\(^4\)\(^-\)\(^10\) Nonetheless, the overall impairment in these studies seems more severe than observed in the present study, where 90% had preserved ambulation without need for support, 4% needed support and 6% were without any walking function after an average duration of disease of 17 years. It seems, therefore, that the long-term prognosis has improved during recent years. The explanation for this improvement most likely is the increased awareness of CIDP, easier access to therapy, and more effective treatment regimens.\(^32\)

An unpublished hospital-based estimate suggests a CIDP prevalence in the Danish population (5.5m) of 4.0 per 100,000 inhabitants as of December 31\(^{\text{st}}\), 2017.\(^33\) This corresponds well with previous epidemiological studies in various parts of the world suggesting a prevalence ranging from 0.8 to 8.9 per 100,000.\(^34\)\(^-\)\(^39\) Only 51 out of the 129 patients had a clinical follow-up, which might increase the uncertainty of the effects of long-lasting immune modulating therapy. However, most of the non-evaluated patients either died of unrelated disease or were excluded due to disabling co-morbidity that would obscure the true impact of long-term CIDP. Moreover, identifying patients using the Danish National Patient register, which includes all contacts to the Danish healthcare system, ensures a representative sample. Since the ICD-10 criteria in Denmark...
were effective from 1994, patients are also included using local registers at all hospitals treating CIDP including electrophysiological records, local databases and invoice details. In this way we included patients treated before 1994. Another potential limitation is the lack of examination of the 16 non-participating patients who neither differed with respect to age, gender, duration of disease, time since first contact, nor duration of treatment. In the 16 non-participating patients 8 had an acute onset type of CIDP, but in the group of studied patients the NIS and I-RODS did not differ between those with an acute onset type (n, 7) and the remaining cohort (n, 44), p-values being 1.0 and 0.8, respectively. The proportion of the acute, GBS-like onset type of CIDP in the examined cohort is in accordance with a previous report that found a 16% occurrence.40

More than half of the patients in the present study developed a stable condition without the need for further immune-modulating therapy, the length of the treatment free period being 7.0 years (IQR: 4.0 – 14.7) following a treatment duration period of 6.4 years (range 0.1-22.0). Similar observations have been reported, elsewhere.6,7 As emphasized in the literature there is a need for regular evaluation of the need for further treatment regardless of the duration of disease.7

At time of disease onset, the latency before initiation of immune-modulating therapy was significantly shorter in those patients who no longer were treated. Therefore, early initiation of immune-modulating therapy might well reduce the treatment duration. The retrospective nature of this study limits the conclusions that can be drawn but raises hypotheses for future studies.

For the primary end-points we found significant disease impact on all scores except for strength of hand grip. Among the secondary end-points, pain, social contact, and amount of paid work were unaffected. These findings show that the vast majority of treated CIDP patients only
have a moderate degree of disability, physical and functional impairments and impairment of quality of life. Nevertheless, for a few treated patients long-term CIDP is still associated with severe morbidity (6%) and even mortality (1%).

The close associations between the I-RODS score and the NIS, and of each of these two scores to isokinetic strength, walking performance and quality of life shows that the physical impairment plays a significant role for the over-all disability in long-term treated CIDP patients. This observation is in accordance with the findings of a world-wide multi-center study including 59 CIDP patients having a mean disease duration of 1.8 years in which clinical parameters were compared to the I-RODS score.41

In accordance with the recommendations of the 196th ENMC international workshop we applied the I-RODS for evaluation of disability.15,42 The degree of impairment found using this scale was in accordance with the results that we obtained with the other scales applied. A similar impairment of the I-RODS score in CIDP as described in our study has been reported elsewhere.43

Isokinetic strength was examined in a previous study of 14 CIDP patients with a median follow-up time of 8.7 years.4 In that study a 20% reduction was reported, similar to that found in the present study. In the present study as well as in the afore mentioned study weakness was most pronounced at the ankle, especially the plantar flexion being affected. Walking function was moderately impaired both using the Timed 25-Foot Walk test and the Six-Spot Step Test. Recognition of weak plantar flexors is clinically difficult and most likely plays a role for the impairment of walking. Attention is drawn to the observation that improvement of strength following exercise training might well have a significant effect on ambulation.44
In the present study fatigue was more pronounced in patients with CIDP than in controls. Analysis of covariance did not show an independent effect of treatment status on fatigue for CIDP patients having the same NIS or I-RODS score, indicating that disease activity does not by itself lead to fatigue.

A clinical important finding is that long-term disability is related to initial delay of therapy. Those patients who had the longest delay of therapy had the most severe long-term disability, suggesting that disability occurring early during the disease course remains despite subsequent therapy. Potential explanations for the delay of treatment are delay of establishment of a diagnosis, delay of referral to appropriate neurological expertise and postponement of a costly treatment decision.

Support for the notion that the long-term prognosis in CIDP is determined early during the course of disease is supported by a 5-year follow-up study in which data did not indicate progression. It is well-known that there is an association between a poor neurological condition in CIDP and axonal damage defined electrophysiologically. A potential explanation for deterioration of the neurological condition during the early phase of disease is, therefore, that irreversible axonal damage occur during a prolonged period without treatment.

In conclusion, overall disability, neurological impairment, dysfunction and reduction of quality of life are milder affected than anticipated, but 10% have a severe impairment of walking function. Based on the findings it is hypothesized that early intervention with immune modulating therapy might well improve the long-term prognosis for CIDP.
Abbreviations

9-HPT = Nine-Hole Peg Test; CIDP = Chronic Inflammatory Demyelinating Polyneuropathy; FSS
= Fatigue Severity Scale; IKS = isokinetic strength; I-RODS = Inflammatory Rasch-built Overall
Disability Scale; MDI = Major Depression Inventory; NIS = Neuropathy Impairment Score; PI-
NRS = Pain-Intensity - Numerical Rating Scale; R-ODS = Rasch-built Overall Disability Scale;
SAS-SR = Social Adjustment Scale – Self Report: Short; SSST = Six Spot Step Test; T25FW =
Timed 25-Foot Walk
References


33. Personal communication to Johannes Jakobsen.


44. Markvardsen LH, Overgaard K, Heje K, Sindrup SH, Christiansen I, Vissing J, et al. Resistance training and aerobic training improve muscle strength and aerobic capacity in...
Published online: January 2018. DOI: 10.1002/mus.25652.
Table 1. Demographics and clinical data in 51 patients with chronic inflammatory demyelinating polyneuropathy and in 20 controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (Inter quartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since CIDP onset (y)</td>
<td>16.0 (14.0 – 21.0)</td>
</tr>
<tr>
<td>Time since first neurology contact (y)</td>
<td>15.0 (13.0 – 19.0)</td>
</tr>
<tr>
<td>Lag time until start of therapy (y)</td>
<td>0.9 (0.3 – 3.0)</td>
</tr>
<tr>
<td>Age at onset (y)</td>
<td>39.0 (30.0 – 49.0)</td>
</tr>
<tr>
<td>Acute, GBS-like onset (n)†</td>
<td>7</td>
</tr>
<tr>
<td>Walking status at first neurology contact‡§/current walking status§ (n)</td>
<td>Walking independently 34/46</td>
</tr>
<tr>
<td></td>
<td>Walking with aids 2/2</td>
</tr>
<tr>
<td></td>
<td>No ambulation 10/3</td>
</tr>
<tr>
<td>Therapy during disease course/current therapy (n)</td>
<td>IgG 50/23§</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids 19/1</td>
</tr>
<tr>
<td></td>
<td>PE 10/1</td>
</tr>
<tr>
<td></td>
<td>Azathioprine 5/1</td>
</tr>
<tr>
<td></td>
<td>Ciclosporine 2/0</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide 1/1</td>
</tr>
<tr>
<td></td>
<td>No treatment 0/27</td>
</tr>
<tr>
<td>Current CDAS (n, %)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Duration of treatment (y)†</th>
<th>Age (y)</th>
<th>Height (m)</th>
<th>Sex, M:F (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Patients</td>
<td>Control</td>
<td>Patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.0 (6.0 – 13.0)</td>
<td>58.0 (46.0 – 68.0)</td>
<td>59.5 (45.5 – 67.5)</td>
<td>37:14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2, 3.9</td>
<td>4, 7.8</td>
<td>1, 2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5, 9.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†One patient without data on onset.
‡Data of 46 patients
§Net amount of individual change of walking status from onset of disease to study participation is insignificant (p = 0.09).
¶Median IgG dose 30.0 g/week (Inter quartile range: 18.0 – 40.0). Twelve patients received subcutaneous IgG and 12 intravenous IgG, one receiving both.
Table 2. Data for the 6 primary end-points in 51 CIDP patients and 20 controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>CIDP</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-RODS score (0 – 100), Median (IQR)</td>
<td>83 (65.0 – 100.0)</td>
<td>100 (93.0 – 100.0)</td>
<td>0.0004*</td>
</tr>
<tr>
<td>NIS (0 – 220), Median (IQR)</td>
<td>23.5 (16.5 – 32.5)</td>
<td>11.3 (4.0 – 18.0)</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>IKS (0 – 100), Mean (95% CI)</td>
<td>70.2 (65.1 – 75.4)</td>
<td>88.0 (81.7 – 94.3)</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Grip strength (kilograms force), Mean (95% CI)</td>
<td>31.3 (27.9 – 34.7)†</td>
<td>36.7 (31.9 – 41.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>T25FW (seconds), Median (IQR)</td>
<td>4.3 (3.7 – 5.5)</td>
<td>3.5 (3.2 – 4.1)</td>
<td>0.001*</td>
</tr>
<tr>
<td>EQ-5D-5L-Index value (0 – 1), Median (IQR)</td>
<td>0.8 (0.7 – 1.0)</td>
<td>1.0 (0.9 – 1.0)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*Significant after Bonferroni correction.
†Data of 50 patients, only.
### Table 3. Secondary end-points in 51 CIDP patients and 20 controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>CIDP</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSS (1 – 7), Mean (95% CI)</td>
<td>3.9 (3.3 – 4.4)</td>
<td>2.6 (2.1 – 3.1)</td>
<td>0.0006</td>
</tr>
<tr>
<td>PI-NRS (0 – 10), Median (IQR)</td>
<td>0 (0 – 1.7)</td>
<td>0 (0 – 1.0)</td>
<td>0.7</td>
</tr>
<tr>
<td>VO₂ max (mL/kg/min), Mean (95% CI)</td>
<td>28.5 (25.1 – 32.5)</td>
<td>35.2 (30.7 – 40.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>SSST (seconds), Median (IQR)</td>
<td>6.0 (5.1 – 8.1)</td>
<td>4.8 (4.2 – 5.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>9-HPT (seconds), Mean (95% CI)</td>
<td>24.2 (21.6 – 27.0)</td>
<td>20.7 (19.4 – 22.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>EQ-5D-5L VAS score (0 – 100), Median (IQR)</td>
<td>80 (60.0 – 90.0)</td>
<td>90 (82.5 – 98.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>MDI (0 – 50), Median (IQR)</td>
<td>5.0 (3.0 – 11.0)</td>
<td>2.0 (1.0 – 5.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>SAS-SR-Short (35 – 90), Mean (95% CI)</td>
<td>43.8 (42.0 – 45.6)</td>
<td>43.9 (41.9 – 46.0)</td>
<td>0.9</td>
</tr>
<tr>
<td>Weekly hours of paid work, Median (IQR)</td>
<td>37 (15.0 – 37.0)</td>
<td>32.5 (8.0 – 37.0)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Results from 34 patients and 19 controls. Four CIDP patients were unable to perform the test.
†Data of 50 patients, only
‡Data of 34 patients and 14 controls under 65 years of age (the age of retirement in Denmark).
**Figure titles and legends:**

Title:
Figure 1. Flowchart for the inclusion of patients

Title:
Figure 2. Univariate regression analysis of the I-RODS score against four of the primary end-points

Legend:
95% confidence interval (grey shading) and prediction limits (area between dashed lines).
NIS = Neuropathy Impairment Score. I-RODS = Inflammatory Rasch-built Overall Disability Scale. IKS = Isokinetic strength.

Title:
Figure 3. Regression of lag-time until treatment against the I-RODS score corrected for age.

Legend:
I-RODS = Inflammatory Rasch-built Overall Disability Scale. IKS = Isokinetic strength.
Search lists: 2,128

Not fulfilling inclusion criteria: 1999
- No evidence for CIDP: 1909
- Untreated CIDP: 5
- 1st contact after 2006: 85

Included: 129

Deceased: 23 (mean age at death: 71.1 y*)
- CIDP: 1 (resp.insuff.)
- Cancer: 10
- Cardiac disease: 5
- Unknown/not registered: 4
- Other: 3

Rejected participation/No study request reply: 16 (mean age: 63.7 y)

Excluded: 39 (mean age: 69.0 y)
- Chemotherapy: 8*
- Diabetes: 12*
- Disabling orthopedic disease: 3*
- Disabling concomitant neurological disease: 4*
- Age > 90: 6*
- Other: 14*

*Some patients meeting several exclusion criteria.
$R^2 = 0.46$, $p < 0.0001$

$R^2 = 0.51$, $p < 0.0001$

$R^2 = 0.45$, $p < 0.0001$

$R^2 = 0.67$, $p < 0.0001$