# Functioning and related determinants in patients with inflammatory and idiopathic polyneuropathy

Het functioneren en hieraan gerelateerde determinanten bij patiënten met inflammatoire en idiopathische polyneuropathie

door

Peter Erdmann

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# Functioning and related determinants in patients with inflammatory and idiopathic polyneuropathy

## Het functioneren en hieraan gerelateerde determinanten bij patiënten met inflammatoire en idiopathische polyneuropathie

(met een samenvatting in het Nederlands)

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Voor pa

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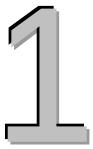

# INTRODUCTION

## FUNCTIONING AND HEALTH

Over past decades, considerable advances have been made in our understanding of chronic illnesses, such as polyneuropathy, and their care and management. A paradigm shift in disease management, moving from treatment of the disease to treatment of the patient[1] , has led to client-centeredness and patient needs[1-5], evidence-based practice[4,6], and disablement/enablement[7-10] becoming central to the clinical decision-making process. In line with this focus on the patient, the consequences of a disease in terms of limitations in activities and restrictions in participation, and health-related quality of life have become important fields of study. Several new theoretical frameworks and models have been developed, based on theories of disease and the consequences of disease on health and functioning.

One framework based on the biopsychosocial model is the International Classification of Impairments, Disabilities, and Handicap (ICIDH)[11], which was developed in 1980 under the aegis of the World Health Organization (WHO). It describes disability in terms of the person and society. The classification was modified in 2001 into the International Classification of Functioning, Disability and Health (ICF)[12,13]. The ICF provides a set of classifications to describe patients' health and health-related states. These health and health-related states are classified into three domains, namely, *body functions and structures* (e.g., pain and muscle strength), *activities* (e.g., walking), and social *participation* (e.g., work), derived from the perspective of the body, the individual, and society (Fig. 1). In the ICF, the term *functioning* refers to all body functions, activities, and participation, while disability refers to all impairments, activity limitations, and participation restrictions. The ICF also lists environmental (e.g., climate and terrain) and personal factors (e.g., age and gender), as contextual factors that may interact with the three domains. The domains and conceptual factors are related to each other, and under certain circumstances and times create a 'disablement process'[7]. Studies of this 'disablement process' provide information about patients' functioning[14-18]. These studies have formed the basis of what nowadays is known as 'disability medicine', a clinical and applied scientific approach that aims to minimize the functional consequences of disease by developing evidence-based treatments for rehabilitation.

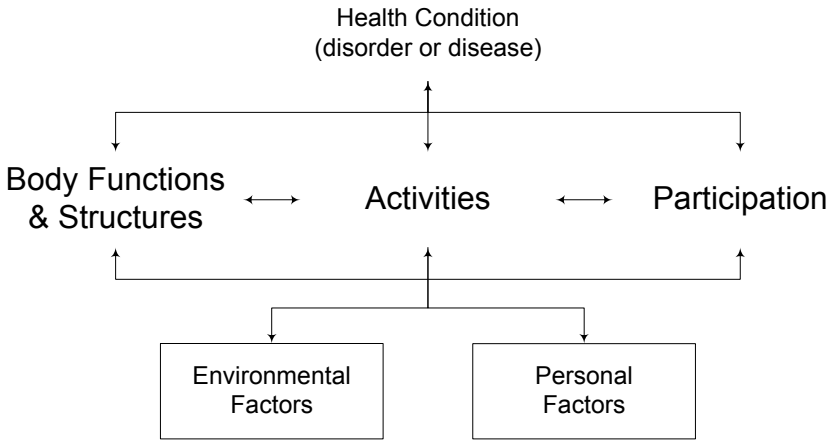


Fig. 1 The International Classification of Functioning, Disability and Health (ICF).

**FUNCTIONING AND HEALTH OF PATIENTS WITH POLYNEUROPATHY**

Until about the 1990s, the focus of most studies of polyneuropathy was on neurological, electrophysiological, or laboratory assessments, so that the effects of medical and pharmacological treatments were mainly evaluated at the level of body functions and structures[19]. Functioning and health-related quality of life were mostly assessed using instruments with broad grading definitions, e.g. the modified Rankin Scale, the Hughes Clinical Grading Scale, and the Short Form-36[19,20]. However, in the 1990s there was a growing awareness that while patients with polyneuropathy had serious problems in functioning, relatively little was known about their health in terms of activities or participation[19,21,22]. Knowledge of a person's level of activities or participation is needed before treatment advice can be given or the effects of medical interventions and/or training on functioning can be measured[21-24]. The relationship between the ICF domains was investigated in patients with Guillain-Barré Syndrome (GBS)[14]. Investigators considered it important that the functional outcomes measured by the instruments used should be meaningful to patients[19,25]. Not the clinician, but the patient was to be central to decisions regarding how to influence and measure functioning and health[4]. This culminated in the development of the first core sets of instruments based on the ICF framework and health-related quality of life[21,25,26]. This approach has been developed further in the last 12 years by a collaborating force of European neurologists with special interest in inflammatory neuropathy, the European Inflammatory Neuropathy Cause and Treatment (INCAT) Group. This group has published several articles on functioning and clinically relevant instruments (plus

their psychometrics) to assess body functions, activities, and participation, and health-related quality of life in patients with GBS and chronic inflammatory demyelinating polyneuropathy (CIDP)[22]. ICF-based functional health profiles of patients with polyneuropathies other than GBS have not been investigated yet, and thus is it not known whether the profiles are similar to those of patients with other (inflammatory) polyneuropathies. Studies of functional health profiles are useful, because they may provide information about potentially beneficial interventions[27-29] and which neuropathy-specific clinimetric instruments should be used in clinical and research settings. In 2004 consensus was reached by the European Neuromuscular Centre for the use of a core set of instruments for various peripheral neuropathies[30]. However, a core set of instruments for CIAP and MMN has not yet been established.

**POLYNEUROPATHY**

The polyneuropathies are a diverse group of diseases affecting the peripheral nerves, mainly in the arm(s) and/or leg(s). Polyneuropathy is the most common neuromuscular disorder, with an estimated prevalence of 500 per 100,000 persons and an estimated incidence of 40 per 100,000 persons per year in the Netherlands[31]. It is usually characterized by symmetrically distributed distal sensory loss ('glove' and/or 'sock' like) and/or muscle weakness of the limbs (hands and/or lower legs/feet). Tendon reflexes can be diminished or absent. The most common causes of polyneuropathy in the Western world are systemic diseases, such as diabetes, or toxic effects of medication and alcohol abuse. Polyneuropathies are classified by their speed of progression (acute vs. subchronic/chronic), type of nerve affected (sensory vs. motor), their pathological substrate (the axon [axonal degeneration], the myelin sheath [segmental demyelinization], or the cell body), and their cause (see Table 1) [31]. The studies of this thesis focus on idiopathic neuropathy (Chronic Idiopathic Axonal Polyneuropathy [CIAP]) and two autoimmune neuropathies (Chronic Inflammatory Demyelinating Polyneuropathy [CIDP], and Multifocal Motor Neuropathy [MMN]).

Tabel 1. Polyneuropathy classification.

| Pathological substrate | Cause | Example |
|---|---|---|
| Cell body | | |
| Axonal degeneration | Hereditary | Hereditary Motor and Sensory Neuropathy type II |
| | Metabolic | Diabetic neuropathy |
| | Deficiency | Vit B1, B12 |
| | Toxic | Drugs, Metal |
| | Infectious | Lyme disease, HIV |
| | Autoimmune | Vasculitic neuropathy |
| | Idiopathic | Chronic Idiopathic Axonal Polyneuropathy |
| Segmental demyelinization | Hereditary | Hereditary Motor and Sensory Neuropathy type I |
| | Autoimmune | Multifocal Motor Neuropathy and Chronic Inflammatoir Demyelinating Polyneuropathy |

**Chronic Idiopathic Axonal Polyneuropathy**

CIAP is a slowly progressive distal symmetric sensory or sensorimotor polyneuropathy accompanied by axonal degeneration [32-34]. Autonomic features are uncommon, but pain is often a major impairment[34]. Clinical symptoms include tingling, dysaesthesia or hyperaesthesia, burning pain, numbness, and muscle weakness. The sensory impairment and muscle weakness may lead to impaired balance, which may adversely influence patients' mobility and dexterity. Tendon reflexes may be diminished or absent. Usually, both large- and small-fibre sensory nerves are affected, leading to a symmetrical decrease in the sense of touch, proprioception, vibration, temperature, and pain. Sensory disturbances develop first in the toes and soles of the feet and extend to the feet and the lower legs in a sock-like distribution. Muscle weakness starts in the toe extensors and ankle dorsiflexors and may extend later to the intrinsic hand muscles and ankle flexors. CIAP is mostly diagnosed in older individuals, with a mean age of onset of 57 years; there is a male predominance[33,34]. About 10–20% of all polyneuropathies (i.e. 50-100 per 100,000 persons) are diagnosed as CIAP[31]. Because the cause of CIAP is unknown and the disease cannot be treated as such, the focus of care is to minimize the functional consequences of the disease.

**Chronic Inflammatory Demyelinating Polyneuropathy and Multifocal Motor Neuropathy**

CIDP is a chronic immune-mediated polyneuropathy in which symmetrical sensory impairment and/or muscle weakness are progressive for more than 12 weeks after onset. Muscle weakness may be distal and proximal in the legs and/or in the arms. The course is relapsing, stepwise progressive, or progressive. CIDP is not accompanied by pain. The tendon reflexes may be diminished or absent. The mean onset of CIDP is 50 years, but it may occur at any age. The reported

prevalence of CIDP varies greatly, from 1.9 to 7.7 per 100,000 persons[35,36]. Patients with CIDP respond to treatment with high-dose intravenous immunoglobulin, corticosteroids, or plasma exchange.

MMN is a chronic immune-mediated neuropathy characterized by slowly progressive, predominantly distal, asymmetric limb weakness in the arms more than the legs, not accompanied by sensory loss. At the time of presentation, muscle weakness is usually present in one (lower) arm or hand. Tendon reflexes are usually diminished. The mean age of onset is 40 years (range 20-70), with a male predominance. In the Netherlands there are about 100 patients with MMN. Patients generally respond well to treatment with high-dose intravenous immunoglobulin, which stabilizes the muscle weakness, although slow progression may occur[37].

## THE AIMS OF THE THESIS

The aim of the studies described in this thesis was to study the functioning of patients with CIDP, MMN, or CIAP, and the determinants of their functioning. Specific research questions were:

1. What are the functional health profiles of patients with different inflammatory polyneuropathies (CIDP and MMN), and do these profiles reveal relevant determinants that can be studied further?
2. How can these determinants be assessed, i.e., what type of clinimetric instruments could be of value in these populations?
3. What are the functional health profiles of patients with CIAP and MMN established with these instruments?
4. What other determinant(s) might influence the functioning of patients with CIAP?

## OUTLINE OF THE THESIS

In chapter 2 the functional health profiles of patients with CIDP and MMN were investigated in a cross-sectional study on the basis of the ICF framework. The problems patients experienced in daily life were used to identify specific determinants of functioning and appropriate performance-based instruments. It was clear that dexterity and walking ability could be determinants of the functioning of patients with polyneuropathy. Because there are no specific instruments to assess dexterity and walking ability in these patients, the Sequential Occupational Dexterity Assessment (SODA) and the modified Shuttle Walk Test (SWT) were

chosen as potentially relevant tests. The SODA has earlier been shown to be a valid tool to assess dexterity in patients with rheumatoid arthritis. Because the SWT was originally developed to assess functional capacity in patients with chronic airway obstruction and heart failure, the test was validated for the assessment of walking ability in patients with CIAP and MMN in the study described in chapter 3.

Subsequently, the functional health profiles of patients with CIAP and MMN were assessed with the SODA and validated SWT in the studies presented in chapters 4 and 5. In addition to the functional health profiles derived from our studies, clinical experience has shown that pain might also be a determinant of the functioning of patients with CIAP. However, little is known about specific aspects of pain and its association with health-related quality of life. The pain patients experience was investigated in detail, using the generic McGill Pain Questionnaire, in the study presented in chapter 6.

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# 2

# FUNCTIONAL HEALTH STATUS OF PATIENTS WITH CHRONIC INFLAMMATORY NEUROPATHIES

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**ABSTRACT**

The functioning of 12 patients with chronic inflammatory demyelinating polyneuropathy (CIDP), and 18 patients with multifocal motor neuropathy (MMN) was evaluated to obtain health profiles and appropriate clinimetric instruments. Assessment was made in a cross-sectional study by means of a performance-based body function test (hand-held dynamometry), two performance-based activity tests (10-Meter Walk Test (10MWT) and Berg Balance Scale (BBS)), a self-reported activity test (Canadian Occupational Performance Measure (COPM)), and a self-reported functioning test (Sickness Impact Profile 68 (SIP68)). In both patient groups, CIDP and MMN, specific health profiles were manifest. A clear relationship between body function, activities and functioning was not found. Therefore, to assess a patient with inflammatory neuropathy, it is recommended to assess body function as well as activities and functioning, and to select appropriate clinimetric instruments specific for each type of neuropathy.

## INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) are auto-immune inflammatory neuropathies. CIDP has a chronic progressive or relapsing-remitting disease course and is characterized by symmetrical proximal and distal muscle weakness and sensory impairment. The clinical hallmarks of MMN are slowly progressive asymmetric weakness and muscle atrophy without sensory loss. Weakness is more prominent in the arms than in the legs and is most pronounced in distal muscles. Patients with CIDP or MMN respond to immunological treatment such as high-dose intravenous immunoglobulin (IVIg)[1,2].

In most studies of patients with CIDP or MMN, the effect of treatment is evaluated at the level of *body function*, e.g. muscle strength. Yet, although affected individuals report serious problems in *functioning*, little is known about their health in terms of *activities* or *participation* (Note: Terminology according the International Classification of Functioning, Disability and Health: ICF [World Health Organization, Geneva, 2001]. Functioning is an umbrella term encompassing all body functions, activities and participation) [3]. Functioning is mostly assessed using instruments with broad grading definitions (e.g. Rankin scale or Hughes Clinical Grading scale). Recently, the 'Medical Outcome Study 36-item short-form health status scale' (SF-36) was recommended[4]. However to measure the effect of treatment in patients with CIDP or MMN on functioning, it may be more appropriate to evaluate a person's level of activities or participation more specifically[5,6,7].

The aims of this study were to evaluate the performance-based and self-reported body function, activities, and functioning of patients with CIDP and MMN to determine whether the diseases have characteristic health profiles and, second, to determine whether body function, activity, and functioning are related in each patient-group. This information can be used to choose clinimetric instruments for general practice and for research purposes specific for each type of neuropathy.

## MATERIALS AND METHODS

### Patients

Patients were included if they fulfilled the established diagnostic criteria for CIDP and MMN[8,9]. Patients with severe concurrent medical disease (e.g., diabetic neuropathy, other neuromuscular disorders, or hartfailure), expected to influence the test results, were excluded. Of all 36 patients with CIDP and MMN who entered the University Medical Center from September 1999 to February 2001, 30

individuals met the inclusion criteria: 12 patients with CIDP and 18 patients with MMN. The clinical features of all participants are presented in Table 1.

**Study design**

The functioning of the 30 patients was evaluated in a cross-sectional study. Demographic data were assessed and all measurements were obtained by one examiner (PGE), who at that time had more than 5 years of clinical experience with the instruments used at the Department of Neurology. All tests were performed just before the patients received a 5-day course of IVIg treatment. Walking ability (10-Meter Walk Test [10MWT])[10] and functional balance (Berg Balance scale [BBS])[11] were assessed as measures of performance-based activities. The 10MWT and BBS were chosen because, in our experience, patients often complain about their limited mobility and balance. The Canadian Occupational Performance Measure (COPM)[12] was chosen as a measure of self-reported activities, and the Sickness Impact Profile 68 (SIP68)[13] was chosen as a measure of self-reported functioning to provide detailed information about the problems patients experienced in everyday life. Finally, in order to relate activities and functioning with body function, muscle strength was tested by means of hand-held dynamometry (HHD).

Table 1. Clinical features of 30 patients with chronic inflammatory neuropathies.

| | CIDP n=12 | MMN n=18 |
|---|---|---|
| Sex (male;female) | 4 ; 8 | 13 ; 5 |
| Age (median;range), years | 53.5 ; 19-79 | 49 ; 30-59 |
| Disease duration (median;range), years | 2.8 ; 0.5-25 | 9 ; 3-19 |
| Affected sites, n (%) | | |
| arms only | 0 | 5 (28) |
| arms>legs | 0 | 8 (44) |
| arms=legs | 5 (42) | 5 (28) |
| legs>arms | 5 (42) | 0 |
| legs only | 2 (16) | 0 |
| Rankin score*, n (%) | | |
| 0 | 0 | 0 |
| 1 | 0 | 0 |
| 2 | 6 (50) | 13 (72) |
| 3 | 6 (50) | 5 (28) |
| 4 | 0 | 0 |
| 5 | 0 | 0 |

CIDP, chronic inflammatory demyelinating polyneuropathy; MMN, multifocal motor neuropathy.
*The group CIDP did not differ statistically from the group MMN on the Rankin scores.

**Instruments**

*Body function*

The maximal isometric strength of the muscles of the arms and legs was measured bilaterally using a MicroFET® hand-held dynamometer (Hoggan Health Industries Inc.). A Jamar® dynamometer (Therapeutic Equipment Co.) was used to measure grip strength. The reliability and validity of these instruments have been found to be good[14,15,16,17]. Muscle strength was measured using the 'make test' of the shoulder (extensors, lateral rotators and abductors), the elbow (flexors and extensors), the wrist (extensors), the hip (flexors and abductors), the knee (flexors and extensors), and the ankle (dorsal flexors), according to Andrews *et al*.[18]. Hand grip strength was measured on both sides, according to Mathiowetz *et al*.[19].

*Activities*

The 10MWT is a validated and responsive test in which the individual is asked to walk over a 10-m course from a standing position at his/her own preferred speed[10,20]. Time is recorded using a stop watch. The mean scores of three tests were used. The BBS, a measure of functional balance[11], consists of 14 items in which the respondent meets certain time or distance requirements, such as times stepping and reaching forward. Each item is graded 0-4. The total score of 56 points can be achieved if the respondent is able to perform the complete test independently and safely. The BBS has been found to be a reliable and valid test in several disease populations[21,22]. The COPM is based on the model of human occupational performance. It implies a semi-structured interview in which the patient is asked to identify problems related to self-care, productivity and leisure. Originally, performance and satisfaction scores on the identified problems are rated on a scale of 1-10 by the patient. We used the instrument to assess functional problems as mentioned by the patients (see *Data analysis*). The COPM has proven to be a valid, reliable, and responsive test in several disease populations (including Guillain-Barré syndrome)[12,23,24,25]. We used the validated, responsive Dutch version of the COPM[26,27].

*Functioning*

The SIP68 is a standardized questionnaire measuring functioning in daily life. It consists of 68 items grouped in six categories. Each item describes a dysfunctional behavior, and respondents indicate whether it applies to them (yes or no). The scores range from 0 to 68, with higher scores representing poorer functioning in daily life. Reliability and validity have been found to be good[28]. The validated Dutch version of the SIP68 was used[29].

**Data analysis**

The Rankin scores between both groups were compared using the Mann-Whitney U test. Descriptive statistics were applied to the 10MWT and BBS data. The problems as mentioned on the COPM were categorized into the relevant sections of the chapter 'Activities and Participation' of 'The International Classification of Functioning, Disability and Health: ICF'[30] (*World Health Organization, Geneva, 2001*). The 10 sections with the highest frequencies were selected, and frequencies of both patient groups were transformed into relative frequencies. Differences between groups were estimated with the Fisher's exact test. For the SIP68, the total scores were calculated as well as the percentage of dysfunctional items per category. In addition, item scores higher than 80% were also recorded. Health profiles were established on the basis of the COPM and SIP68 scores. Muscle strength z-scores were calculated by means of reference values for healthy adults[19,31], and data reduction was performed by calculating mean z-scores for the shoulders, elbows, wrists/hand grip, hips, knees, and ankles. Sum scores were calculated for the arms ( shoulders + elbows + wrists/hand grip) and legs (hips + knees + ankles) and a total sumscore for all extremities. Differences between groups were estimated with the Mann-Whitney U test (10MWT, BBS, SIP68) and Student t test (HHD). Because of the small sample size, we did not adjust for differences in age and sex. The Spearman's rank correlations between the 10MWT, the BBS, the SIP68 'total' and the SIP68 'motor control' sub-category, and the muscle strength sum scores scores within groups were also calculated. Analyses were performed using the Statistical Package for Social Sciences (version 11.5). All tests were two-sided and p values $< 0.05$ were considered significant.

**RESULTS**

**Body function**

The z-scores were calculated for the 12 patients with CIDP and 15 patients with MMN (Table 2). No significant differences were found between the groups. The weakest muscles in the patients with CIDP were those of the knee and ankle regions. The muscles of the arms and hip region were moderately weak. A clear proximal-to-distal decrease in muscle strength was seen in the legs of CIDP patients. For patients with MMN, a clear proximal-to-distal decrease in muscle strength was seen in both the arms and the legs, with the muscles of the ankle region being the weakest.

Table 2. Muscle strength z-scores (hand-held dynamometry mean [±SD]) of patients with chronic inflammatory neuropathies.

| | HHD | |
|---|---|---|
| | CIDP n=12 | MMN n=14 |
| Shoulder | -1.06 (±1.42) | -1.62 (±1.14) |
| Elbow | -0.84 (±1.94) | -1.91 (±1.46) |
| Wrist/grip | -1.51 (±1.81) | -2.43 (±1.26) |
| Sum score arms | -1.12 (±1.61) | -1.94 (±1.11) |
| Hip | -0.82 (±1.37) | -0.70 (±1.34) |
| Knee | -2.15 (±1.66) | -1.78 (±1.34) |
| Ankle | -3.14 (±1.34) | -2.96 (±1.01) |
| Sum score legs | -1.73 (±1.31) | -1.54 (±1.11) |
| Total score arms and legs | -1.35 (±1.42) | -1.79 (±1.05) |

HHD, hand-held dynamometry; CIDP, chronic inflammatory demyelinating polyneuropathy; MMN, multifocal motor neuropathy.

**Activities**

Eleven of the patients with CIDP and 13 of the patients with MMN performed the 10MWT (Table 3). Patients with CIDP were significantly slower than those with MMN (p=0.019). The time scores within the group of CIDP patients varied substantially, whereas the MMN group showed less variation in scores and had a median time score (8.4 s) similar to that of healthy adults. Twelve patients with CIDP and 12 patients with MMN performed the BBS test (Table 3). MMN patients had a significantly better functional balance score than CIDP patients (p=0.024). The scores of the CIDP group showed considerable variation. Two patients with CIDP had a maximal best score of 56. More than 50% of the CIDP patients experienced problems (score ≤ 3) with the following four items: *standing with eyes closed, reaching forward with outstretched arms, standing with one foot in front,* and *standing on one foot*. The patients with MMN had almost optimal scores, with four patients having maximum scores (56 points). More than 50% of the MMN patients experienced difficulties (score ≤ 3) with only one item: *reaching forward with outstretched arms*. The total number of different problematic activities that the patients reported at the COPM interview was 53 for the 12 patients with CIDP, and 87 for the 18 patients with MMN. The number of sections in which these activities were classified was 34 for CIDP and 44 for MMN. The 10 largest sections are presented in Fig. 1. Walking long distances (section *walking*) (92%) and stair climbing (section *climbing*) (67%) accounted for most of the problems experienced by the patients with CIDP. Most patients with MMN experienced problems related to arm and hand use, especially buttoning up clothes (section *putting on clothes*)

(78%), writing (72%), all kinds of manipulations with the hands (72%), handling a key or jar (section *turning or twisting the hands or arms*) (67%), and cutlery use (section *eating*) (61%). Significant differences between groups were detected for the following sections: walking (p=0.018, in favour of CIDP), driving motorized vehicles (p=0.018, in favour of CIDP), driving human-powered transportation (p=0.018, in favour of CIDP), manipulation (p=0.008, in favour of MMN), shopping (p=0.006, in favour of CIDP), maintaining a standing position (p=0.006, in favour of CIDP), sports (p=0.004, in favour of MMN), using writing machines (p=0.004, in favour of MMN), eating (p=0.001, in favour of MMN), and putting on footwear (p=0.001, in favour of MMN). Post hoc analysis with Bonferroni correction showed that only eating (p=0.017) and putting on footwear (p=0.017) were different between groups.

**Functioning**

Table 3 summarizes the SIP68 scores of 11 patients with CIDP and 18 patients with MMN. The percentage of dysfunctional items for each of the six categories of the SIP68 is shown in Fig. 2. The highest percentage of dysfunctional items for the patients with CIDP was found in the category *motor control* (51%), in which most items are related to walking, climbing stairs, and functional balance. Three items were scored by more than 80% of the patients with CIDP (see Fig. 2 legend). In patients with MMN, the highest percentage of dysfunctional items was 31% (category *motor control*). The percentage of abnormal items on the category *psychological autonomy and communication* was due to one item only (*I am having trouble writing or typing*). This item and the item related to difficulty in doing handwork in the category *motor control* were scored by more than 80% of the patients with MMN (see Fig. 2 legend). Significant differences between groups were found on the SIP68 subcategories *motor control* (p=0.025) and *psychological autonomy and communication* (p=0.028).

**Correlation between performance-based and self-reported tests**

The scores on the performance-based tests and the self-reported tests were significantly correlated in three instances in patients with CIDP (Table 4). First, patients with high BBS scores had low 10MWT scores (r=-0.76, p=0.007). This means that the better the functional balance, the better the ability to walk. Second and third, patients with high BBS scores reported low SIP68 and SIP68 'motor control' scores meaning that a better functional balance goes with a better health-related functional status and functional motor control (r=-0.62, p=0.04 and r=-0.71, p=0.014, respectively). One significant correlation was found in the MMN group:

patients with higher 10MWT scores had higher SIP68 'motor control' scores (r=0.59, p=0.036). This means that the worse the ability to walk, the worse the functional motor control.

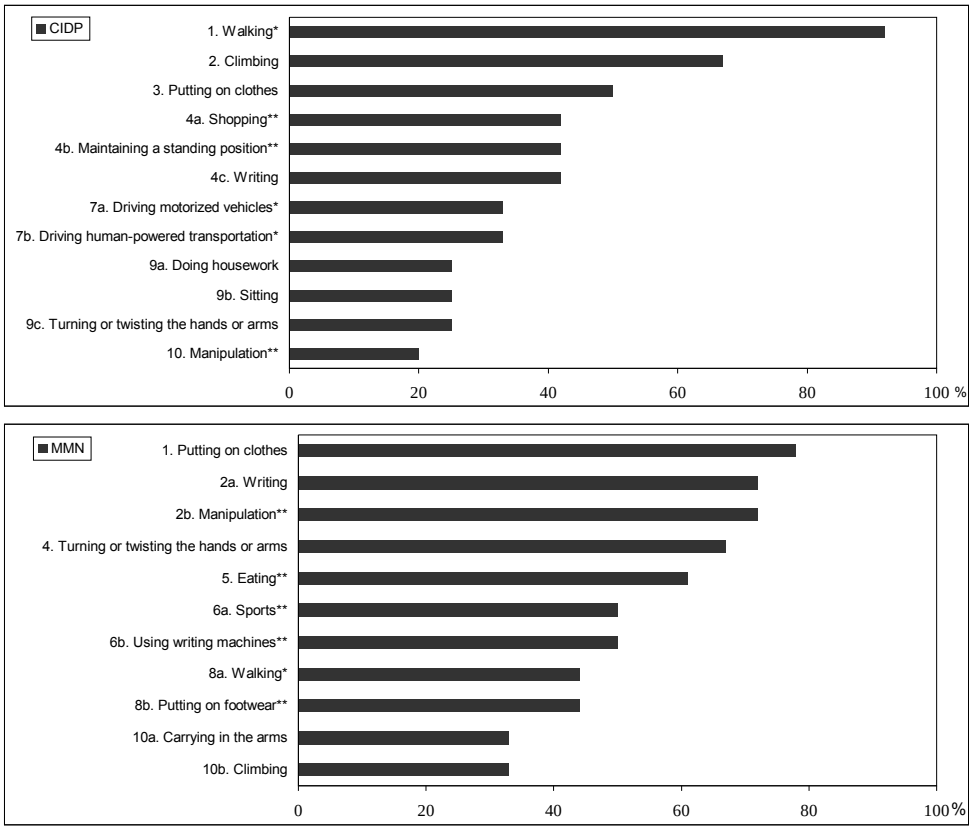


Fig. 1 Top 10 frequency scores of the Canadian Occupational Performance Measure of patients with chronic inflammatory neuropathies. Sections corresponding to the International Classification of Functioning, Disability and Health: ICF. CIDP, chronic inflammatory demyelinating polyneuropathy (n=12); MMN, multifocal motor neuropathy (n=18). *Differences significant at the 0.05 level; **differences significant at the 0.01 level.

**Table 3.** Scores on the 10-Meter Walk Test (s), the Berg Balance scale (points), and the Sickness Impact Profile 68 (points) of patients with chronic inflammatory neuropathies.

| | 10 MWT* | | BBS* | | SIP68 | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | SOM AUT | | MOTOR* | | PSYCH AUT* | | SOC BEH | | EMOT STAB | | MOB RANGE | | TOTAL | |
| | CIDP | MMN | CIDP | MMN | CIDP | MMN | CIDP | MMN | CIDP | MMN | CIDP | MMN | CIDP | MMN | CIDP | MMN | CIDP | MMN |
| | n=11 | n=13 | n=12 | n=12 | n=11 | n=18 | n=11 | n=18 | n=11 | n=18 | n=11 | n=18 | n=11 | n=18 | n=11 | n=18 | n=11 | n=18 |
| Median | 11.3 | 8.4 | 52.5 | 55 | 1 | 1 | 6 | 4 | 0 | 1 | 3 | 3 | 0 | 0 | 0 | 0 | 10 | 9 |
| P25 | 8.9 | 7.8 | 39 | 55 | 0 | 0 | 4.5 | 2 | 0 | 1 | 2.5 | 1 | 0 | 0 | 0 | 0 | 8.5 | 6 |
| P75 | 13.5 | 9.5 | 55 | 56 | 2.5 | 1 | 7.5 | 5.8 | 1 | 1.8 | 3.5 | 3.8 | 0.5 | 0.8 | 3 | 0.8 | 16.5 | 10.8 |
| Range | 7-20.6 | 6.8-10.1 | 13-56 | 50-56 | 0-4 | 0-3 | 3-11 | 1-7 | 0-1 | 0-4 | 0-8 | 0-6 | 0-1 | 0-3 | 0-6 | 0-3 | 8-28 | 2-19 |

10MWT, 10-Meter Walk Test; BBS, Berg Balance scale; SIP68, Sickness Impact Profile 68; SOM AUT, somatic autonomy; MOTOR, motor control; PSYCH AUT, psychological autonomy and communication; SOC BEH, social behaviour; EMOT STAB, emotional stability; MOB RANGE, mobility range; TOTAL, total SIP68 score; CIDP, chronic inflammatory demyelinating polyneuropathy; MMN, multifocal motor neuropathy; P25, 25th percentile; P75, 75th percentile. *Difference between groups is significant at the 0.05 level (two tailed).

Tabel 4. Spearman's rank correlation coefficients of patients with chronic inflammatory neuropathies.

| | 10MWT | BBS | SIP68 | SIP68 motor | HHD arms | HHD legs | HHD total |
|---|---|---|---|---|---|---|---|
| 10MWT | | | | | | | |
| CIDP | | -0.76** (n=11) | 0.36 (n=10) | 0.55 (n=10) | 0.17 (n=11) | -0.05 (n=11) | 0.16 (n=11) |
| MMN | | -0.07 (n=12) | 0.51 (n=13) | 0.59* (n=13) | -0.13 (n=13) | -0.23 (n=13) | -0.18 (n=13) |
| BBS | | | | | | | |
| CIDP | | | -0.62* (n=11) | -0.71* (n=11) | -0.42 (n=12) | -0.13 (n=12) | -0.40 (n=12) |
| MMN | | | -0.12 (n=12) | 0.06 (n=12) | 0.43 (n=12) | 0.58 (n=12) | 0.32 (n=12) |
| SIP68 | | | | | | | |
| CIDP | | | | | -0.03 (n=11) | -0.06 (n=11) | -0.03 (n=11) |
| MMN | | | | | -0.19 (n=14) | -0.51 (n=14) | -0.28 (n=14) |
| SIP68 motor | | | | | | | |
| CIDP | | | | | 0.12 (n=11) | 0.21 (n=11) | 0.12 (n=11) |
| MMN | | | | | 0.04 (n=14) | -0.35 (n=14) | -0.11 (n=14) |

10MWT, 10-Meter Walk Test; BBS, Berg Balance scale; SIP68, Sickness Impact Profile 68; SIP68 motor, Sickness Impact Profile 68 'motor control' subcategory; HHD, hand-held dynamometry; CIDP, chronic inflammatory demyelinating polyneuropathy; MMN, multifocal motor neuropathy.

*Correlation coefficient is significant at the 0.05 level (two tailed); **correlation coefficient is significant at the 0.01 level (two tailed).

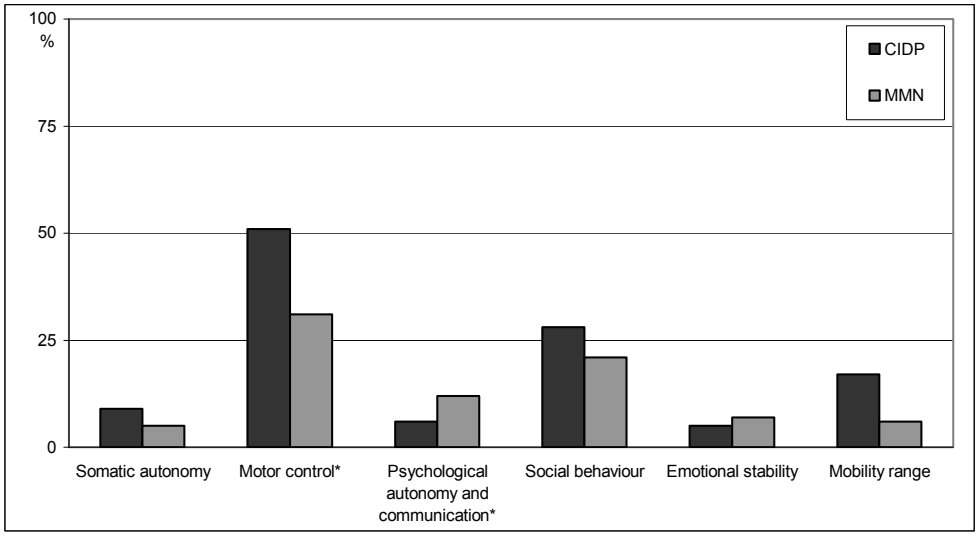


Fig. 2 Percentage of dysfunctional items over the six categories of the Sickness Impact Profile 68 of patients with chronic inflammatory neuropathies. The following items were scored by >80% of the patients: CIDP: I walk more slowly (n=11, category motor control); I go up and down stairs more slowly, for example, one step at a time, stop often (n=10, category motor control); I am not doing heavy work around the house (n=9, category social behaviour). MMN: I have difficulty doing handwork, for example turning faucets, using kitchen gadgets, sewing, carpentry (n=17, category motor control); I am having trouble writing or typing (n=16, category psychological autonomy and communication). CIDP, chronic inflammatory demyelinating polyneuropathy (n=11); MMN, multifocal motor neuropathy (n=18). *Differences between groups significant at the 0.05 level.

## DISCUSSION

The aim of this study was to describe performance-based and self-reported body functions, activities, and functioning of a group of patients with CIDP and MMN, in

order to obtain health profiles and to obtain information for the development of a set of tailored clinimetric instruments. In general, the outcome of the COPM and SIP68 provided useful information about the functional health status of the patients, whereas the results obtained with the 10MWT and BBS emphasized specific problems in patients with CIDP, but not in patients with MMN.

Some remarks can be made of the performance-based tests. The 10MWT and BBS seem suitable tests for our patients with CIDP, but show ceiling effects in patients with MMN. That is, the problems related to walking and keeping balance were not detected by these instruments because the overall muscle strength of the legs of MMN patients was hardly affected. Also, patients with CIDP frequently suffer from sensory impairments which may influence gait velocity or functional balance, while patients with MMN do not suffer from sensory impairment. Bohannon *et al*.[32] described reference values for comfortable walking speed in healthy adults (age range 20-70 years). He found mean walking speed scores of 1.27-1.46 m/s. Two (18%) of our patients with CIDP and five (38%) patients with MMN had walking speeds within or below this range. Besides the statistical difference between CIDP and MMN, we think that the difference in outcome on the 10 MWT is clinically relevant.

Concerning the self-reported tests, the problems the patients with CIDP reported most often on the COPM and SIP68 are related to their mobility. On the COPM, problems in walking long distances and climbing stairs were most frequently mentioned. This corresponded with the frequently marked items of the category *motor control* of the SIP68. The distribution of the scores on the SIP68 resembles the scores of a group of patients (n=114) on the SF-36 by Merkies *et al*.[4]. However, most of these patients (mean disease duration 6.8 years, range 0.5-28 years) had Guillain-Barré syndrome (73%) and only 20% had CIDP. While our patients with CIDP tended to experience problems associated with the legs, the patients with MMN mostly complained of problems with arm and hand functioning. The disability profile of the latter patient group was quite similar to that reported in a study by Taylor *et al*.[33], in which 32 patients with MMN (median disease duration 7.3 years, range 0.7-25.4 years) were interviewed by telephone. They also found the manipulation of objects with the fingers (picking up coins, writing, turning a key, or using a knife and fork) to be the most commonly and most severely affected. Walking was affected in about one-third of the patients whereas it was affected in 44% of our patients with MMN (Fig. 1). The arm/hand dysfunctioning together with the difficulty in walking may explain the relatively high score on the category *motor control* on the SIP68, however, these problems did not seem to affect patients' experienced *somatic autonomy* or *social behavior* to a great extent (Fig. 2).

We found a moderate relationship between the SIP68 total scores and SIP68 motor control scores on the one hand and the BBS scores on the other in our patients with CIDP. A clear relationship between muscle strength and the outcome on the 10MWT and BBS and muscle strength and the SIP68 scores was not found. This is in accordance with the results by Merkies *et al*.[34]. In their study, impairment measures (MRC sum score) explained only about half of the variance in 'handicap' (Rotterdam nine-items handicap scale) ($R^2$=0.52), while 'disability' measures (10MWT and Nine-hole peg test) showed a stronger association with 'handicap' ($R^2$=0.76). It could therefore be argued that the tests evaluate different aspects of one's health. This means that it is not sufficient to measure only muscle strength in patients with inflammatory neuropathies. Rather, such measurements should be complemented by measuring functioning in terms of activities and participation to receive an idea of a patient's health status.

The question remains which instruments should be used. In none of the published studies of CIDP and MMN did the authors justify or explain their choice of instruments used. Molenaar *et al*.[35] suggested that the psychometric properties of currently described instruments should be evaluated (e.g., the Hauser Ambulation Index, the modified Rankin scale, and the Rivermead Mobility Index) rather than that new instruments should be developed. Merkies *et al*.[4] chose the SF-36 due to the lack of availability of a neuropathy-targeted 'quality of life' measure. We believe that clinimetric strategies have to be developed to evaluate activities and functioning of patients with inflammatory neuropathies. On the basis of the functional health profiles we found, we recommend the 10MWT and the BBS, together with HHD and sensory assessment, be used for patients with CIDP, whereas HHD and a test of arm/hand functioning should be used for patients with MMN. A performance-based functional test of interest might be the Sequential Occupational Dexterity Assessment[36] because the instrument items resemble the problems of hand functioning of our patients with MMN. In the current study, some patients with CIDP and MMN performed the 10MWT with ease, which is consistent with them experiencing difficulties only with walking long distances. For this reason, an extended walking test should be used as well. Here, the Shuttle Walk Test[37] could probably serve as a useful performance-based functional instrument. In addition, reliability, validity, and responsiveness must be assessed in patients with inflammatory neuropathies, especially in patients with MMN. Also, clinimetric strategies have to be developed for patients who are not able to walk 10 meters or patients who are wheelchair bound. In this way, a standard set of instruments can be developed to assess functioning and the effect of therapy at different stages of the inflammatory process. An example of such a set of instruments has already

been given by Dal Bello-Haas *et al*.[6] for patients with amyotrophic lateral sclerosis (ALS).

In conclusion, this study demonstrated specific health profiles in patients with inflammatory neuropathies. A clear relationship between body function, activity, and functioning could not be demonstrated. Therefore, to assess a patient with inflammatory neuropathy, body function, activity, and functioning should be evaluated. The 10MWT and BBS are useful to assess patients with CIDP, whereas an extended walking test and an arm/hand functioning test are needed to assess patients with CIDP and MMN. These results may be helpful to choose appropriate clinimetric instruments for general practice and for research purposes specific for each type of neuropathy.

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# 3

# FUNCTIONAL ASSESSMENT OF WALKING ABILITY IN PATIENTS WITH POLYNEUROPATHY: VALIDATION OF THE SHUTTLE WALK TEST

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Submitted

**ABSTRACT**

The aim of the study was to assess the face and concurrent validity of the Shuttle Walk Test (SWT) for evaluating the walking ability of patients with chronic idiopathic axonal polyneuropathy (CIAP, n=41) and multifocal motor neuropathy (MMN, n=49). The main outcome measures were: [A] face validity: whether patients considered the 10 Meter Walk Test (10MWT) and the SWT to reflect walking in daily life (Likert scale; 1= not at all, 10=very well) and whether symptoms experienced after the SWT were similar to those experienced in daily life; [B] concurrent validity: 10MWT, the SWT, the Fatigue Severity Scale (FSS), and the RAND-36 domain physical functioning (RAND-36-PF). The mean (SD) score for how well the 10MWT and SWT reflected daily walking ability was 6.8 (1.3) and 7.4 (1.6) (n.s.), respectively, in patients with CIAP and 6.9 (1.2) and 7.9 (1.0) (p=0.001), respectively, in patients with MMN. Spearman rank correlations between the 10MWT and the SWT ranged -0.70 to -0.82 for most patients in the two groups; patients with MMN who walked at 'normal' speed (based on normative data) during the 10 MWT had a score of -0.21. The correlation between the SWT and the RAND-36-PF ranged from 0.40 to 0.65 in both patient groups. The correlation between the two walking tests and the FSS was ≤ 0.27. The SWT is a valid instrument to assess walking ability and related complaints in patients with CIAP and MMN.

## INTRODUCTION

One of the major problems in patients with polyneuropathy is their limited walking ability[1-4], and especially their ability to walk long distances, such as when hiking or shopping, but there is no gold standard method for assessing the walking ability of these patients in a performance-based manner. The generic 10 Meter Walk Test (10MWT)[5,6] is frequently used[7-13], but often shows ceiling effects[2,9,10,13], i.e., the walking ability of patients over short distances (10 meter) is comparable to that of healthy adults[14,15], and has poor responsiveness in patients with inflammatory polyneuropathies[9].

We have found in the clinic that patients with polyneuropathy can often perform the 10MWT with ease (like 'normal walkers') and only experience problems after walking long distances. Thus an extended walking test, such as the incremental Shuttle Walk Test (SWT), may be more appropriate for assessing the walking ability of these patients[2]. The SWT was developed to measure the functional capacity of patients with chronic airway obstruction[16], but its clinimetric properties have since been established in patients with chronic heart failure, COPD, and intermittent, claudication[17-26]. Reference values for maximum walking distance have been established for healthy men aged 50 to 70 years[27]. Validation of this test for measuring the walking ability of patients with polyneuropathy requires assessment of both functional capacity and walking ability, to ensure that patients' walking performance reflects limitations due to their neurological disease rather than, for example, impaired cardiopulmonary fitness. We have previously found the SWT to be feasible in patients with chronic idiopathic axonal polyneuropathy (CIAP) and multifocal motor neuropathy (MMN)[3,28,29], two polyneuropathies studied in our department. CIAP is a slowly progressive distal symmetric sensory or sensorimotor polyneuropathy with axonal degeneration that mainly affects the legs. In these patients, known causes of polyneuropathy have been excluded by extensive laboratory examination. The mean age of onset of CIAP is 57 years, with a male predominance[10,30]. MMN is a chronic immune-mediated neuropathy characterized by slowly progressive, predominantly distal asymmetric limb weakness, in the arms more than the legs, not accompanied by sensory loss. The mean age of onset is 40 years, with a male predominance[31].

The aim of this cross-sectional study was to assess the face and concurrent validity of the SWT for measuring the walking ability of patients with CIAP and patients with MMN.

## MATERIALS AND METHODS

### Patients

Forty-one clinically stable patients diagnosed with CIAP and 49 clinically stable patients with MMN who attended the outpatient clinic of the Department of Neuromuscular Diseases of the University Medical Center Utrecht, the Netherlands, between 2007 and 2009 participated in this study. The choice for CIAP and MMN as representatives of polyneuropathy was made because patients with these disorders are subject to long-term follow-up research in our department. All participants gave informed consent. Data collection was approved by the ethics committee of the University Medical Center Utrecht.

### Measurements

*Walking ability*

In the 10MWT, the patient is asked to walk over a 10-meter course from standing still at their preferred walking speed, using a walking aid if needed[5]. Normative data for walking speed have been determined for healthy adults[14,15]. The time taken to walk the distance is recorded using a stop-watch. In our study, the patients started walking after a countdown, and the rater walked beside the patient. The test stopped immediately after a patient stepped onto or over the 10-meter line. We calculated the mean time scores of three assessments.

In the incremental SWT, the patient is asked to walk around a 10-meter course marked by two cones placed 9 meters apart, thus allowing 0.5 meter for turning at each end (Fig. 1). Walking speed is regulated by pre-recorded metronomic signals. The patient is asked to turn around the cones at each signal. In the original version of the SWT, the initial walking speed of 1.8 km/h (0.50 m/s) increases by 0.6 km/h (0.17 m/s) every minute up to a maximum walking speed of 8.5 km/h (2.37 m/s). We used a modified version in which the initial walking speed of 3.0 km/h (0.83 m/s) increases by 0.5 km/h (0.14 m/s) every 2 minutes up to a maximum walking speed of 7.0 km/h (1.94 m/s)[32]. This modification was made in order to allow patients to adapt to walking at each speed and probably mimics walking long distances in daily life. Standardized instructions were given before the assessment and the patients are encouraged to walk for as long as they could without risking falling, overfatigue, or pain. The use of walking aids (including orthopedic shoes and ankle-foot orthoses) was permitted. The test was terminated by the examiner if the patient could not complete the 10-meter course, which meant that the subject's foot was not on or within a line placed at 0.5 meter from the cone at the pre-recorded signal and the patient was not able to make up this delay in the next three shuttles, if the patient stopped walking the shuttles for

whatever reason, or if the patient completed the entire test (i.e. 150 times the 10-meter course). The number of shuttles (i.e. 10-meter courses) was noted after test completion. Higher numbers are indicative of a better performance (i.e., walking ability), with a maximum of 1500 meters (see appendix).

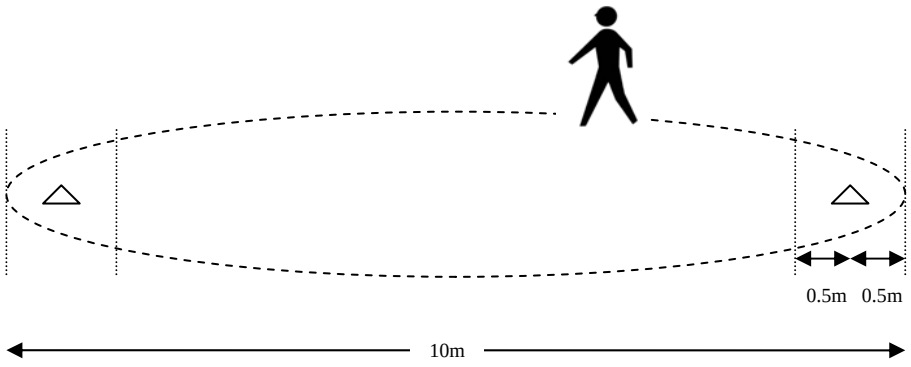


Fig. 1 The Shuttle Walk Test.

*Fatigue*

We measured self-reported fatigue using the validated Dutch version of the Fatigue Severity Scale (FSS). The FSS[33] is a brief nine-item self-report questionnaire with answers ranging from 1 ('strongly disagree') to 7 ('strongly agree') for each item. The mean score for the nine items ranges from 1 ('no signs of fatigue') to 7 ('most disabling fatigue'); the normative score is 2.3 in healthy adults[33], whereas a score higher than 5.0 is indicative of severe fatigue[34]. Examples of the test items are: 'Fatigue interferes with my physical functioning' and 'Fatigue is among my three most disabling symptoms'. The FSS possesses good psychometric properties in patients with inflammatory polyneuropathies[34], and the internal consistency has been found to be good in patients with CIAP and MMN[28,29].

*Physical functioning*

The RAND-36[35] is a generic multidimensional questionnaire to assess health-related quality of life and is equivalent to the MOS Short Form-36[36]. It comprises eight domains, assessing eight health concepts. The scores for each domain are coded, summed, and transformed into a scale ranging from 0 to 100, where 100 is the best possible rating. For this study, the 10-item domain 'physical functioning' (RAND-36-PF) was scored. The responses on three items were analyzed

separately: the patients were asked whether they could walk more than 1 km, 0.5 km, and 100 m (3-point Likert scale responses; 1=very much impaired, 2=slightly impaired, 3=not impaired). We used the validated, reliable and internally consistent Dutch version of the RAND-36[37,38].

**Design and data analysis**

The study had a cross-sectional design. Patients came to the outpatient clinic, where demographic data, comorbidities, medication use, and use of walking aids were recorded and patients were classified into subgroups, using the Modified Rankin Scale[39] (Table 1). The patients performed the 10MWT and the SWT to assess concurrent validity. There was a 5-minute interval between tests, which was long enough to allow patients to recover from the exertion. Tests were performed in the gymnasium of the outpatient clinic. Heart rate and perceived exertion (measured with the Borg scale) were measured immediately before and after the SWT, but not before and after the 10MWT, because in the latter patients do not have to exert themselves maximally. The Borg scale[40] is a 12-point Likert scale for perceived exertion, with scores ranging from 0 ('nothing at all') to 10 ('very, very strong'). Face validity was assessed by means of patient interview after completion of the two walking tests. Self-reported fatigue and perceived physical functioning were assessed with the FSS questionnaire and the RAND-36-PF questionnaire, respectively. Patients had been sent the questionnaires earlier and were asked to complete them the day before the tests. The questionnaires were checked for completeness in the presence of the patients. All measurements were performed by one examiner (PGE), who has more than 10 years of clinical experience with these patient groups and with the instruments used.

*Face validity*

Data on the symptoms patients experienced after completing the SWT and whether the 10MWT or the SWT reflected patients' walking ability in daily life were analyzed. Patients were asked: 'how well does the 10MWT and the SWT reflect your walking ability in daily life? Please score each test, with scores ranging from 1 (not at all) to 10 (very well)'.

*Concurrent validity*

Spearman's rank correlation analyses were performed on the outcome of the 10MWT and the SWT to determine the concurrent validity. For this purpose, both patient groups were categorized into patients who had normative time scores on the 10MWT ('normal' walkers), and patients who had higher than normative time

scores on the 10MWT ('slow' walkers). In this way it would be possible to detect differences in correlation coefficients between the two groups, and hence differences in the assessment of walking ability with the two tests. The SWT might be particularly useful for assessing the walking ability of patients who walk at normal speed on the 10MWT. Differences in correlation coefficients between these two groups were investigated with bootstrap analysis[41]. Patients were assumed to be 'normal' walkers whenever their time scores were within 2 standard deviations of the mean normative score[14] or within the 95% confidence interval[15]. Also, correlation analyses were performed between outcome on the SWT, the FSS, and the RAND-36-PF to evaluate the concurrent validity of the SWT for assessing walking ability.

Walking ability might be influenced by gender, age, height, and the use of walking aids. Subanalysis by means of hierarchical multiple univariate linear regression analysis (enter procedure) was therefore carried out to investigate the contribution of each of these determinants. To this end, the outcome on the SWT was used as dependent variable and the outcome on the 10MWT, gender, age, height, and walking aids as independent variables. The relative importance of the independent variables is expressed as a statistical significant standardized coefficient beta. Analyses were performed using the Statistical Package for Social Sciences (version 15.0). All tests were two-sided and P values $< 0.05$ were considered significant.

## RESULTS

Six patients with CIAP were excluded from the study because they were unable to perform the SWT because of neuropathic pain in the lower legs or feet (5 patients) or impaired balance (1 patient). Their mean (SD) 10 MWT score of 24.9 seconds (9.5) was higher than that of the CIAP study group (9.7 seconds (2.5)) ($p<0.05$). All excluded patients used walking aids. In the MMN group all patients were able to perform the SWT.

Demographics, comorbidity, and the use of walking aids are presented in Table 1. About two-thirds of the patients were classified as Rankin 2, i.e. 'slight disability: unable to carry out all previous activities but able to look after own affairs without assistance'. Five patients with CIAP and one patient with MMN had two or more comorbidities. Four patients with CIAP and two patients with MMN were taking beta-adrenergic blocking agents. Five CIAP patients and two MMN patients used a combination of orthopedic shoes/ankle-foot orthoses and walking aids. Test results are presented in Table 2. One patient with CIAP and one with MMN could

Table 1. Demographic characteristics, co-morbidities and use of walking aids.

| Demographics | CIAP n=41 | MMN n=49 |
|---|---|---|
| Age | 66.2 (9.6) | 51.5 (11.1) |
| Gender (m/f) | 30/11 | 35/14 |
| Disease duration | 6.5 (5.3) | 2.0 (0.6) |
| Modified Rankin Scale score | | |
| 0 | 0 | 1 |
| 1 | 2 | 6 |
| 2 | 33 | 32 |
| 3 | 6 | 10 |
| 4 | 0 | 0 |
| | | |
| Heart failure | | |
| hypertension | 6 | 1 |
| arrhythmia | 3 | 0 |
| angina pectoris | 2 | 1 |
| valvular heart disease | 0 | 2 |
| COPD | 3 | 3 |
| Diabetic | 0 | 1 |
| Ankylosing spondylitis | 0 | 1 |
| Lumbar disc herniation | 5 | 1 |
| Low back pain | 2 | 1 |
| Total hip prothesis | 2 | 0 |
| Cruciate ligament/meniscus | 1 | 2 |
| Ankle fracture | 0 | 1 |
| Cerebrovascular incident | 1 | 0 |
| Depression | 3 | 0 |
| | | |
| Walking aids | | |
| ankle-foot orthosis | 6 | 7 |
| orthopedic shoes | 5 | 3 |
| walking-cane | 8 | 0 |
| crutch | 1 | 0 |
| rollator | 2 | 1 |

Values are means (SD) or frequencies.

CIAP, chronic idiopathic axonal polyneuropathy; MMN, multifocal motor neuropathy.

walk maximally 10 meters (one shuttle) in the SWT. Nine CIAP patients and 18 MMN patients had normal walking time scores on the 10MWT (<8 seconds). The distribution of walking tests scores for each patient group and linear line fit are presented in Figures 2, 3, and 4.

**Face validity**

The Likert scores for how well the 10MWT and the SWT reflected daily walking ability are presented in Table 2. In general, more patients (58% with CIAP and 59% with MMN) considered the SWT to better reflect their daily walking ability than the

Table 2. Outcome on the 10MWT, SWT, FSS, and RAND-36-PF.

| Test | | CIAP n=41 | MMN n=49 |
|---|---|---|---|
| 10MWT | Score (sec) | 9.7 | 8.6 |
| | | (2.5) | (2.1) |
| | Representativeness of test (0-10 points) | 6.8 | 6.9* |
| | | (1.3) | (1.2) |
| SWT | Score (n) | 62.6 | 90.1 |
| | | (46.9) | (41.9) |
| | Representativeness of test (0-10 points) | 7.4 | 7.9* |
| | | (1.6) | (1.0) |
| | Reason for stop (n) | | |
| | did not reach cone | 32 | 37 |
| | test completed | 6 | 6 |
| | patient stop | 3 | 6 |
| | Complaints at stop (n) | | |
| | legs 'blocked' | 23 | 24 |
| | fatigue legs | 6 | 5 |
| | balance/stumbling | 0 | 3 |
| | painful legs | 4 | 0 |
| | muscle strength impairment | 0 | 3 |
| | cramp legs | 0 | 1 |
| | normal transition to running | 1 | 6 |
| | fall | 1 | 0 |
| | exhaustion | 0 | 1 |
| | no complaints (i.e. test completed) | 6 | 6 |
| | Heart rate before SWT (beats/min) | 73.2 | 71.7 |
| | | (13.4) | (10.8) |
| | Heart rate after SWT (beats/min) | 103.8 | 111.9 |
| | | (20.0) | (18.7) |
| | Exertion before SWT (Borg score 0-10 points) | 2 | 1 |
| | | (0-8) | (0-4) |
| | Exertion after SWT (Borg score 0-10 points) | 4 | 3 |
| | | (1-10) | (1-7) |
| FSS | Score (1-7 points) | 5.2 | 4.8 |
| | | (1.8-7.0) | (1.4-7.0) |
| RAND-36-PF | Score (0-100) | 50 | 70 |
| | | (0-95) | (5-100) |

Values are means (SD) or medians (range) unless stated otherwise. 10MWT, 10 Meter Walk Test; SWT, Shuttle Walk Test; FSS, Fatigue Severity Scale; RAND-36-PF, RAND-36 domain physical functioning. CIAP, chronic idiopathic axonal polyneuropathy; MMN, multifocal motor neuropathy.

* Significant difference (p=0.001) between the scores for the 10MWT and SWT given by the patients with MMN.

10MWT: they had mean time scores on the 10MWT of 9.7 and 7.7 seconds, respectively. All patients stated that the symptoms they experienced after completion of the SWT were similar to those experienced in daily life. This was not the case for the 10 MWT. In contrast, 38% of the patients with CIAP and 20% of the patients with MMN considered the 10MWT to better reflect their daily walking ability than the SWT; they had mean time scores on the 10 MWT of 11.2 and 9.4 seconds, respectively.

Twenty-three (56%) CIAP patients and 24 (49%) MMN patients felt that their legs 'blocked' after termination of the SWT, i.e. they could not move their legs any faster but did not experience this as a natural transition to running (Table 2).

Another symptom was a sensation of fatigue in the legs, which was mentioned by six patients with CIAP and five patients with MMN. Heart rate and Borg scores were low after the SWT, indicating that the patients did not have to exert themselves maximally when performing the test (maximal cardiopulmonary capacity was not reached). This is supported by post-hoc analysis showing that no patient reached the predicted 80% heart rate score of their calculated maximal heart rate[44]. Only one patient ended the test because of perceived exhaustion (Table 2). The six patients in each group who were able to complete the SWT did not report walking disability in daily life: they had mean scores on the three items related to walking ability on the RAND-36-PF of 2.7, 2.8, and 3.0 in the CIAP group, and 2.8, 3.0, and 3.0 in the MMN group, respectively.

**Concurrent validity**

Table 3 shows the correlation coefficients of the 10MWT and the SWT for the 'normal' walkers and the 'slow' walkers. The correlation was high for all patients with CIAP and for 'slow' walkers with MMN. This means that patients who walked faster on the 10MWT walked further (more shuttles) on the SWT. The correlation was low for the patients with MMN who walked at 'normal' (i.e., normative) speed.

Table 3. Spearman correlation coefficients for the 10MWT and SWT.

| | Walking performance on the 10MWT | | |
|---|---|---|---|
| Group | normal | slow | p-value |
| CIAP n=41 | -0.83 | -0.82 | p>0.10 |
| MMN n=49 | -0.21 | -0.70 | p=0.05 |
| Total n=90 | -0.46 | -0.80 | p=0.03 |

CIAP, chronic idiopathic axonal polyneuropathy; MMN, multifocal motor neuropathy;
normal walkers, patients who walked at normative speed on the 10MWT;
slow walkers, patients who walked slower than normative speed on the 10 MWT.

Correlation coefficients for 10MWT or SWT outcomes on the one hand and RAND-36-PF outcomes on the other ranged from 0.40 to 0.65 (Table 4), which means that there was a moderate association between performance on the walking tests

and patient's perceived physical functioning. There were no great differences between the two walking tests and between the two patient groups. The correlation between walking test scores and FSS scores was low in both patient groups, which means that walking ability was not associated with patient fatigue.

Hierarchical multiple univariate linear regression analysis showed that the 10MWT and age had significant beta values of -0.66 and -0.20 in the CIAP group, and -0.53 and -0.33 in the MMN group. The beta values for gender, height, disease duration, and the use of walking aids were less than 0.10. Therefore, the 10MWT and age contributed most to the explained variance in SWT walking ability.

Table 4. Spearman correlation coefficients for the 10MWT, SWT, FSS, and RAND-36-PF.

| | CIAP n=41 | | MMN n=49 | |
|---|---|---|---|---|
| Test | 10MWT | SWT | 10MWT | SWT |
| FSS | 0.10* | 0 | 0.27* | -0.22* |
| RAND-36-PF | -0.55 | 0.56 | -0.53 | 0.53 |
| >1000m | -0.54 | 0.52 | -0.58 | 0.59 |
| 500m | -0.61 | 0.65 | -0.43 | 0.43 |
| 100m | -0.57 | 0.56 | -0.45 | 0.40 |

Spearman correlation coefficients $p<0.01$ (* n.s.).

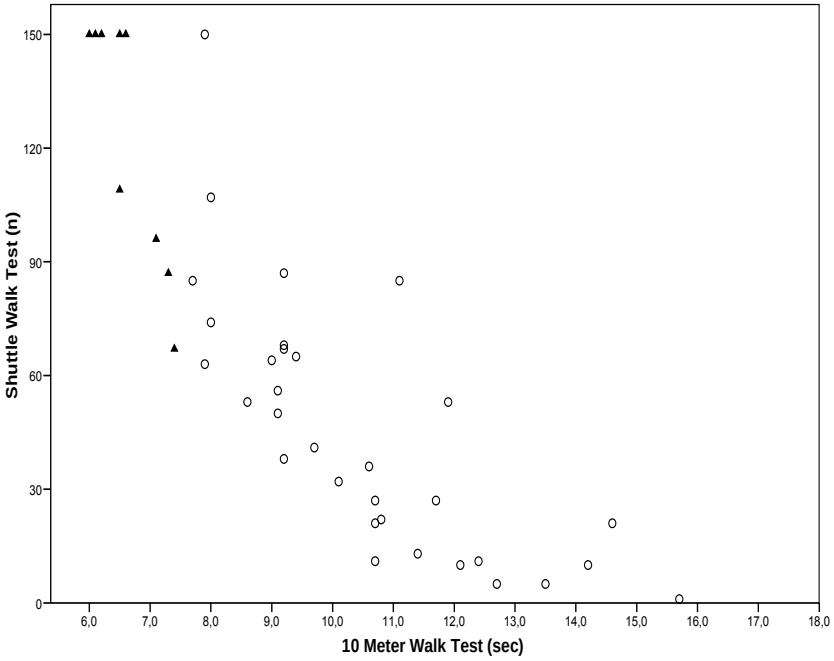


Fig. 2 Distribution of scores on the 10MWT and the SWT of 41 patients with CIAP. ▲= patients walking at normative speed, ○ = patients walking slower than normative speed. Normative values see text.

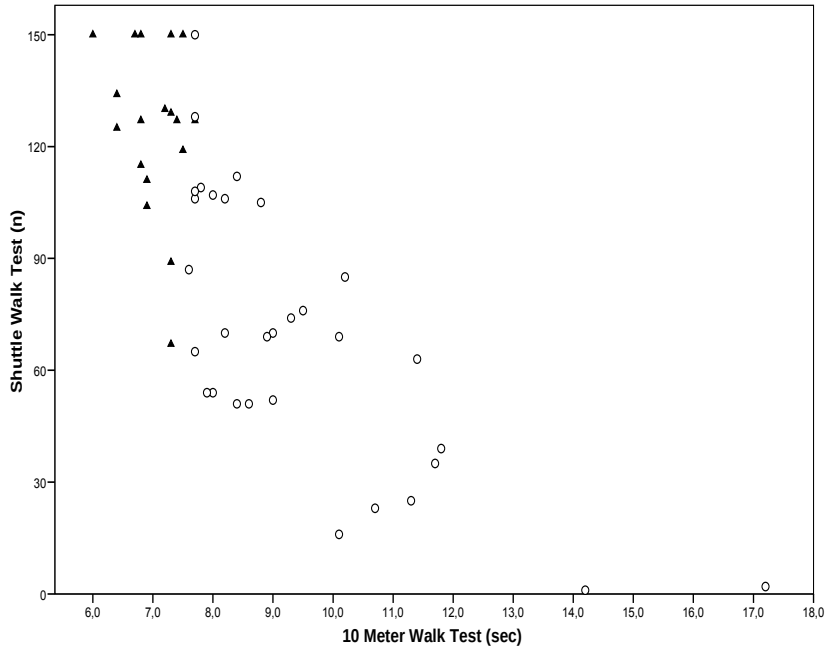


Fig. 3 Distribution of scores on the 10MWT and the SWT of 49 patients with MMN. ▲= patients walking at normative speed, ○ = patients walking slower than normative speed. Normative values see text.

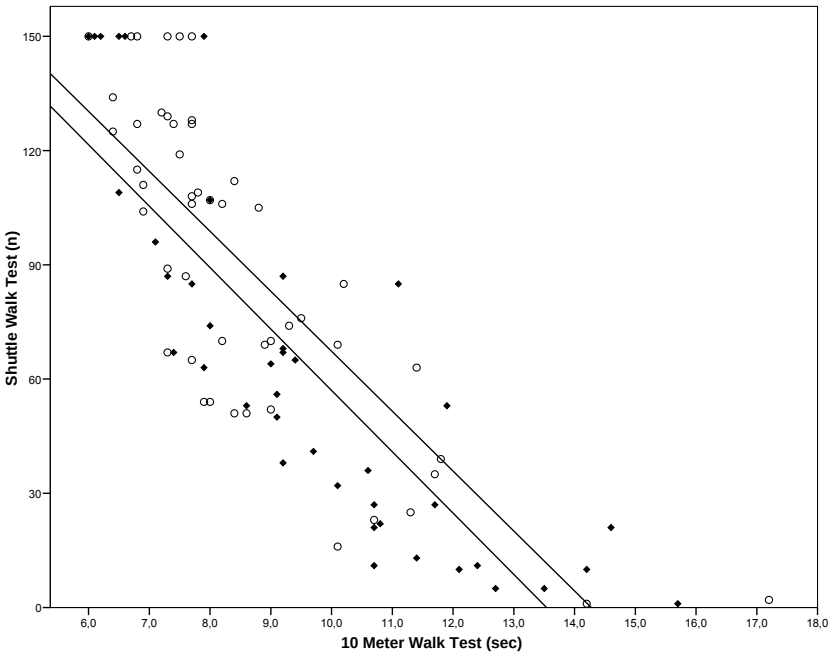


Fig. 4 Distribution of scores on the 10MWT and the SWT of 41 patients with CIAP and 49 patients with MMN. ♦ = CIAP (lower regression line), ○ = MMN (upper regression line).

## DISCUSSION

To our knowledge, this is the first detailed study to assess the walking ability and related symptoms of patients with CIAP and MMN. Walking ability was successfully assessed with the SWT, without showing large floor and ceiling effects, and showed that most patients with CIAP and MMN had walking disability and related symptoms. These problems were not expected in the patients with MMN, because these patients typically have major problems with dexterity not walking ability[2]. Overall, the SWT scores correlated well with the 10MWT scores. The patients considered the SWT to best reflect their daily walking ability, and the symptoms they experienced after performing the SWT mimicked those experienced in daily life. Thus the SWT would appear to be a clinically useful instrument to assess walking ability in patients with polyneuropathy.

Up till now, questionnaires have been designed to assess the walking ability of patients with polyneuropathy[4]. However, patients' rating of their performance may differ quite a bit from their actual performance[3,42]. In our study, patients' perception of their walking ability, as assessed with the RAND-36-PF,

correlated moderately with their performance on the 10MWT and the SWT. Therefore, performance-based instruments such as the 10MWT and especially the SWT can be used to measure the walking ability of patients with polyneuropathy. An alternative performance-based test might be the 6-minute walking test. This test was originally developed to assess functional capacity, and has been used to assess the walking ability of patients with diabetic neuropathy[43]. We chose the SWT because this test is more standardized[25] and is less influenced by encouragement by the rater[21] in patients with chronic heart and lung diseases. Also, the total distance walked in the 6-minute walking test is variable in the two initial assessments[21]. In general, these problems are considered to be of less influence in the SWT[17].

The concurrent validity of the SWT for assessing walking ability was established with the 10MWT. The FSS scores and the SWT scores were poorly correlated, meaning that SWT performance was not influenced by fatigue. The symptoms experienced by the patients after the SWT ('blocking legs' and 'fatigued legs') may have been caused by their neural pathology, but could also have been caused by an impaired oxidative capacity of the muscles due to deconditioning, medication use, aging, or poor nutritional status, as has been described in lung transplantation patients[45]. Therefore, additional research is warranted to investigate the association between patients' symptoms during walking – as in the SWT – and their neuropathology.

Compared to the 10MWT time scores, the SWT time scores of the 27 'normal' walkers showed substantial variation in both patient groups (1.5 seconds on the 10MWT and nearly 60 sec on the SWT) (Fig. 3). Thus the SWT may be more sensitive to changes, but this needs to be confirmed in a properly performed sensitivity-to-change study[46]. It was not possible to measure the SWT performance of subjects who took longer than 12 seconds to complete the 10MWT. Future studies should investigate whether a starting walking speed on the SWT of 2.0 km/h and/or 2.5 km/h is more appropriate in these patients.

This study showed that the SWT is useful for measuring the walking ability of patients with CIAP and MMN, especially those who walk at the same speed as healthy controls (i.e. time scores about 9 seconds or lower on the 10MWT) and for investigating the symptoms elicited by walking long distances. The 10 MWT may be helpful when time scores higher than 9 seconds are expected. The SWT may serve as a performance-based diagnostic test and help guide tailoring of immunological and rehabilitation interventions. The SWT may also be useful in other polyneuropathies and may be complementary to validated tests recommended by the European Inflammatory Neuropathy Cause and Treatment

Group (INCAT) study group[47]. In conclusion, in this study we established the face and concurrent validity of the SWT for assessing the walking ability of patients with CIAP and MMN. The SWT also seems helpful as a performance-based test, inducing the same walking-related symptoms experienced in daily life. Future studies should assess the reliability and responsiveness of the test and establish normative values for patients with polyneuropathies and healthy subjects of different ages.

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# APPENDIX

Shuttle Walk Test

Name:

Date:

Walking aid:

No. of Shuttles:

Patient stopped test / patient did not reach cone in time / patient walked all 150 shuttles*

Reason test termination:

| Speed | Time | Score | Speed | Time | Score | Speed | Time | Score |
|---|---|---|---|---|---|---|---|---|
| 3 km/h | 0:00:00 | 0 | 5,0 km/h | 0:08:05 | 51 | 6,5 km/h | 0:13:58 | 105 |
| **(level 1)** | 0:00:12 | 1 | **(level 5)** | 0:08:12 | 52 | **(level 8)** | 0:14:03 | 106 |
| | 0:00:24 | 2 | | 0:08:19 | 53 | | 0:14:09 | 107 |
| | 0:00:36 | 3 | | 0:08:27 | 54 | | 0:14:14 | 108 |
| | 0:00:48 | 4 | | 0:08:34 | 55 | | 0:14:20 | 109 |
| | 0:01:00 | 5 | | 0:08:41 | 56 | | 0:14:25 | 110 |
| | 0:01:12 | 6 | | 0:08:48 | 57 | | 0:14:31 | 111 |
| | 0:01:24 | 7 | | 0:08:55 | 58 | | 0:14:36 | 112 |
| | 0:01:36 | 8 | | 0:09:03 | 59 | | 0:14:42 | 113 |
| | 0:01:48 | 9 | | 0:09:11 | 60 | | 0:14:47 | 114 |
| 3,5 km/h | 0:02:00 | 10 | | 0:09:18 | 61 | | 0:14:53 | 115 |
| **(level 2)** | 0:02:10 | 11 | | 0:09:25 | 62 | | 0:14:58 | 116 |
| | 0:02:20 | 12 | | 0:09:32 | 63 | | 0:15:04 | 117 |
| | 0:02:30 | 13 | | 0:09:40 | 64 | | 0:15:09 | 118 |
| | 0:02:40 | 14 | | 0:09:47 | 65 | | 0:15:15 | 119 |
| | 0:02:50 | 15 | | 0:09:54 | 66 | | 0:15:20 | 120 |
| | 0:03:00 | 16 | 5,5km/h | 0:10:01 | 67 | | 0:15:26 | 121 |
| | 0:03:10 | 17 | **(level 6)** | 0:10:07 | 68 | | 0:15:31 | 122 |
| | 0:03:20 | 18 | | 0:10:14 | 69 | | 0:15:37 | 123 |
| | 0:03:30 | 19 | | 0:10:20 | 70 | | 0:15:42 | 124 |
| | 0:03:40 | 20 | | 0:10:27 | 71 | | 0:15:48 | 125 |
| | 0:03:50 | 21 | | 0:10:33 | 72 | | 0:15:53 | 126 |
| 4 km/h | 0:04:00 | 22 | | 0:10:40 | 73 | 7 km/h | 0:15:59 | 127 |
| **(level 3)** | 0:04:09 | 23 | | 0:10:46 | 74 | **(level 9)** | 0:16:04 | 128 |
| | 0:04:17 | 24 | | 0:10:53 | 75 | | 0:16:09 | 129 |
| | 0:04:26 | 25 | | 0:11:00 | 76 | | 0:16:14 | 130 |
| | 0:04:35 | 26 | | 0:11:06 | 77 | | 0:16:20 | 131 |
| | 0:04:44 | 27 | | 0:11:12 | 78 | | 0:16:25 | 132 |
| | 0:04:53 | 28 | | 0:11:19 | 79 | | 0:16:30 | 133 |
| | 0:05:02 | 29 | | 0:11:25 | 80 | | 0:16:35 | 134 |
| | 0:05:11 | 30 | | 0:11:32 | 81 | | 0:16:40 | 135 |
| | 0:05:20 | 31 | | 0:11:38 | 82 | | 0:16:45 | 136 |
| | 0:05:29 | 32 | | 0:11:45 | 83 | | 0:16:50 | 137 |
| | 0:05:38 | 33 | | 0:11:51 | 84 | | 0:16:56 | 138 |
| | 0:05:47 | 34 | 6,0 km/h | 0:11:58 | 85 | | 0:17:01 | 139 |
| | 0:05:56 | 35 | **(level 7)** | 0:12:04 | 86 | | 0:17:06 | 140 |
| 4,5 km/h | 0:06:05 | 36 | | 0:12:10 | 87 | | 0:17:11 | 141 |
| **(level 4)** | 0:06:13 | 37 | | 0:12:16 | 88 | | 0:17:16 | 142 |
| | 0:06:21 | 38 | | 0:12:22 | 89 | | 0:17:22 | 143 |
| | 0:06:29 | 39 | | 0:12:28 | 90 | | 0:17:27 | 144 |
| | 0:06:37 | 40 | | 0:12:34 | 91 | | 0:17:32 | 145 |
| | 0:06:45 | 41 | | 0:12:40 | 92 | | 0:17:38 | 146 |
| | 0:06:53 | 42 | | 0:12:46 | 93 | | 0:17:43 | 147 |
| | 0:07:01 | 43 | | 0:12:52 | 94 | | 0:17:48 | 148 |
| | 0:07:09 | 44 | | 0:12:58 | 95 | | 0:17:53 | 149 |
| | 0:07:17 | 45 | | 0:13:04 | 96 | | 0:17:59 | 150 |
| | 0:07:25 | 46 | | 0:13:10 | 97 | | | |
| | 0:07:33 | 47 | | 0:13:16 | 98 | | | |
| | 0:07:41 | 48 | | 0:13:22 | 99 | | | |
| | 0:07:49 | 49 | | 0:13:28 | 100 | | | |
| | 0:07:57 | 50 | | 0:13:34 | 101 | | | |
| | | | | 0:13:40 | 102 | | | |
| | | | | 0:13:46 | 103 | | | |
| | | | | 0:13:52 | 104 | | | |

# 4

# FUNCTIONING OF PATIENTS WITH CHRONIC IDIOPATHIC AXONAL POLYNEUROPATHY (CIAP)

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**ABSTRACT**

Although patients with Chronic Idiopathic Axonal Polyneuropathy (CIAP) report a slow deterioration of sensory and motor functions, the impact of this deterioration on daily functioning has not yet been investigated in detail. The first aim of this cross-sectional study involving 56 patients with CIAP was, therefore, to assess patients' functioning with use of the International Classification of Functioning, Disability and Health (ICF). The second aim was to find determinants of walking ability, dexterity, and autonomy. Fatigue and limited walking ability were present in most patients and differed considerably. In regression models, age, muscle strength, and fatigue together explained 63% of the variance in walking ability, which by itself explained almost 50% of the variance in patients' autonomy indoors and outdoors (42% and 49%, respectively). Muscle strength and sensory function scores together explained 30% of the variance in dexterity scores, which in turn explained only 13% of the variance in autonomy indoors. The diminished autonomy of patients with CIAP might be improved by reducing fatigue, by means of training, and by improving walking ability.

## INTRODUCTION

Even after extensive clinical evaluation and long term follow up, a cause of chronic axonal polyneuropathy cannot be found in 10-18% of patients[1], and in these cases the disorder is termed Chronic Idiopathic Axonal Polyneuropathy (CIAP)[2,3]. The mean age of onset of CIAP is 57 years, with a male predominance. The patients have slowly progressive sensory and motor impairments, and some patients experience neuropathic pain[4]. The impact of these progressive impairments and pain on functioning has not been investigated in detail. Functioning is mostly assessed using instruments with broad grading definitions (e.g. Rankin Scale). As the cause of CIAP is unknown, treatment of the disease itself is not possible. Exercise therapy is often advised, but the benefits on functioning have not been studied.

According to the International Classification of Functioning, Disability and Health (ICF) of the World Health Organization, functioning encompasses (the interactions of) all body functions and structures (e.g. muscle strength), activities (e.g. walking ability), and social participation, taking into account personal (e.g. gender, age) as well as environmental factors (e.g. workplace, assistant devices)[5] (Fig. 1). Studies of functioning may provide information about which interventions may be beneficial[6-8]. For patients with CIAP it is our assumption that fatigue, walking ability, and dexterity may play a determinant role in patients' autonomy.

The first aim of this study was to assess the functioning of patients with CIAP, with use of the ICF. The second aim was to investigate which body functions (muscle strength, sensory function, pain, fatigue, and balance) best explain variance in activity scores (walking ability and dexterity) and participation (autonomy), as well as which activities best explain variance in participation scores.

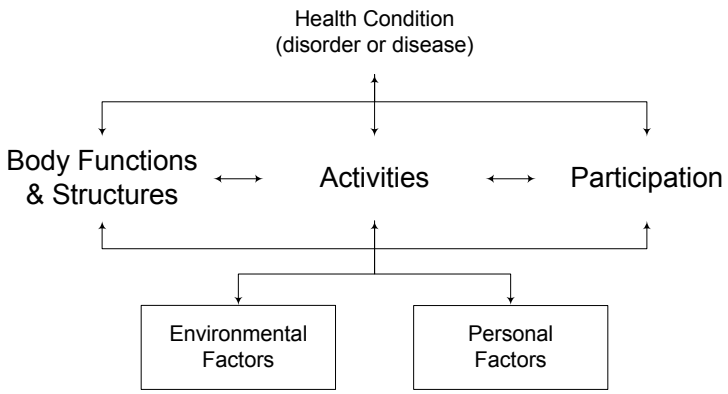


Fig. 1 Interactions between the components of the International Classification of Functioning, Disability and Health (ICF).

## MATERIALS AND METHODS

### Patients

Fifty-six clinically stable patients diagnosed with CIAP[2], identified from a database of the outpatient clinic of the Department of Neuromuscular Diseases of the University Medical Center Utrecht, the Netherlands, were invited to participate in the study when they came for their annual check-up. All patients agreed to have their data anonymously entered into the database. The ethics committee of the UMC Utrecht confirmed that no formal approval for the use of anonymous clinical databases is needed.

### Design

The functioning of the 56 patients was evaluated in a cross-sectional study from September to December 2003. All measurements were taken by two examiners (LLT [neurological examination] and PGE [performance-based tests]). Both investigators had more than 5 years of clinical experience with this patient group and with the instruments used. First, demographic data were registered and patients were classified into subgroups using the Modified Rankin Scale (MRS)[9]. Secondly, functioning of the arms and legs (maximal isometric muscle strength, sensory function, presence of pain [yes/no], dexterity, walking ability, and the use of walking aids [i.e. rollator, crutches, cane, ankle-foot orthosis] [yes/no]) were investigated, as well as patients' self-reported fatigue, balance disorders, and self-reported autonomy indoors and outdoors. The choice of the instruments used was based on the clinical spectrum of CIAP[2,7,10] and guided by the current views and opinions of the ICF. All assessments were done in a quiet and comfortable room at our outpatient clinic except for walking performance, which was assessed in the gymnasium of the outpatient clinic. Patients were sent the Fatigue Severity Scale (FSS) and Impact on Participation and Autonomy (IPA) questionnaires a week before they came to the clinic and were asked to complete them the day before the assessments were done. The questionnaires were checked in the presence of the patients.

### Measurements

*Maximal isometric strength*

The maximal isometric strength of the muscles of the arms and legs was measured bilaterally using a MicroFET® hand-held dynamometer (Hoggan Health Industries Inc., Draper, Utah, USA). A Jamar® dynamometer (Therapeutic Equipment Co., Clifton, New Jersey, USA) was used to measure handgrip strength. The reliability and validity of measurements taken with these instruments are good[11-13]. Muscle

strength was measured using the 'make' test of the shoulder abductors, the elbow flexors, the wrist extensors, the hip abductors, the knee extensors, and the ankle dorsal flexors bilaterally, according to Andrews *et al*.[14]. Handgrip strength was measured twice on each side, according to Mathiowetz *et al*.[15], and the highest score for each side was noted.

*Sensory function*

Touch, pinprick, vibration, and joint position sense were rated according to the distal to proximal distribution of abnormalities, using the Sensory Modality Sum score (SMS)[16]. Summing the scores of all modalities yields a maximum arm sensory sum score and a maximum leg sensory sum score of 28 each.

*Dexterity*

The Sequential Occupational Dexterity Assessment (SODA) is a reliable and valid, performance-based test[17] in which dexterity is measured in 12 standardized tasks, such as writing, cutlery use, and picking up coins. Eighteen items are scored, with scores ranging from 0 (unable to perform the task) to 6 (able to perform the standardized task without difficulty). The range of scores on the SODA is thus 0 to108. The SODA was chosen because this is a bimanual dexterity test, with task items problematic to patients with CIAP.

*Walking ability*

Because it is our experience that patients with CIAP frequently suffer from walking long distances, walking ability was assessed with a modified incremental Shuttle Walk Test (SWT)[18]. Patients were asked to walk around a 10-m course marked by two cones placed 9 m apart, thus allowing 0.5 m for turning at each end. Walking speed was regulated by pre-recorded metronomic signals. The patients were asked to turn the cones at each signal. The initial walking speed was 3 km/hour but was increased by 0.5 km/hour every 2 minutes; the maximum walking speed was 7.0 km/hour. Standard instructions were given before the test and respondents were encouraged to walk as long as they could without risking falling, overuse, or pain. The use of walking aids was permitted. The test was stopped, and the number of shuttles (i.e. 10-m courses) was noted, if patients reported severe complaints (e.g. pain or fatigue), if the patient could no longer complete the 10-m course (the subject was not within 1m of the cone at the pre-recorded signal), or when the patient completed the test (150 times the 10-m course). Higher numbers indicate better performance on the test, with a maximum of 1500 m. The patients were asked why they stopped if they did not complete the test. The SWT is a

reliable, valid, and responsive test in different patient populations[19,20]. Reference values for maximum walking distance for healthy men[21] (n=32) aged 50 to 70 years of the original SWT range from mean (SD) 699 (122) m to 727 (161) m.

*Fatigue*

The Dutch validated version of the FSS[22] was selected as a measure of self-reported fatigue. The FSS is a brief nine-item self-report questionnaire with answers ranging from 1 ('strongly disagree') to 7 ('strongly agree') for each item. The mean score for the nine items ranges from 1 ('no signs of fatigue') to 7 ('most disabling fatigue') and the norm score is 2.3 points in healthy adults[22]. The FSS possesses good psychometric properties[22,23].

*Balance*

The Berg Balance Scale (BBS)[24] consists of 14 items in which subjects have to complete tasks relating to balance within a certain time or cover a certain distance, such as times stepping and reaching forward. Each item is graded 0-4. The maximum score is 56 points. The cut-off score between healthy elderly individuals who can or cannot walk safely and independently without the need of walking aids or supervision is 45 points[25]. The use of walking aids was not allowed, excluding ankle-foot orthoses and orthopedic shoes. The BBS, a reliable and valid test in different populations[25,26], was selected because patients with CIAP frequently report balance disorders.

*Autonomy*

The IPA[27] is a generic, reliable, and valid self-assessment questionnaire[28,29] that measures perceived participation in social life. It contains five subscales with 31 items (autonomy indoors [7 items], autonomy outdoors [5 items], family role [7 items], social relations [6 items], and work and education [6 items]). Each item is graded on a 5-point rating scale with discrete responses, ranging from 0 (very good) to 4 (very poor). Each subscale is scored separately and is expressed in relative scores, with lower scores representing a better autonomy. In this study, the subscales autonomy indoors ($IPA_{indoors}$) and autonomy outdoors ($IPA_{outdoors}$) were used because these scales contain items related to self-care, mobility indoors, the frequency of having social contacts, leisure, and mobility outdoors, items which depend to a great extent on the individuals' general functional mobility.

### Data analysis

Descriptive statistics were used to assess functioning. Scores were calculated for the whole group, as well as subgroups determined by MRS scores. We calculated muscle strength Z-scores using reference values for healthy adults[15,30]. Data reduction was performed by calculating mean Z-scores for the arms (Z-scores for shoulders, elbows, and wrists/handgrip), and the legs (Z-scores for hips, knees, and ankles). The internal consistency of the SMS, SODA, FSS, BBS, and $IPA_{indoors}$ and $IPA_{outdoors}$ was also assessed.

We analyzed the associations between variables in two consecutive steps. First, correlation analyses (Pearson's r) were performed between single body functions, activities, and participation outcome measures, as well as personal and environmental factors (Fig. 1). Then hierarchical multiple univariate linear regression analysis (stepwise procedure) was carried out to investigate which body functions (muscle strength, sensory function, pain, fatigue, and balance) best explain variance in activity scores (walking ability and dexterity) and participation (autonomy), as well as which activities best explain variance in participation scores. We adjusted for age and the use of walking aids. The strength of the association between the dependent variable and the independent variables is expressed as a percentage (adjusted $R^2$ x 100), and the relative importance of the independent variables is given as a standardized coefficient beta. Analyses were performed using the Statistical Package for Social Sciences (version 11.5). All tests were two-sided and P values < 0.05 were considered significant.

## RESULTS

Demographic characteristics and functional outcome measures of all participants are presented for the whole group, as well as for the MRS subgroups (Table 1). The internal consistency of the SMS, SODA, FSS, BBS, and $IPA_{indoors}$ and $IPA_{outdoors}$ in this study was good (Cronbach's α: 0.87, 0.87, 0.95, 0.95, 0.94, and 0.87 respectively).

### Functional outcome measures

Dexterity was only slightly affected in the whole group and in the subgroups. The test items *handling a spoon*, *buttoning a blouse*, *writing a sentence*, and *picking up coins* had the lowest mean scores.

With regard to leg functioning, the mean scores on the SWT varied widely (range 0-150). Different reasons were given for stopping the SWT: 40 patients could not reach the last cone on time, and these patients complained about tired

legs (14 patients), 'blocking' of the legs (i.e. the legs could not move the body faster without pain, cramp etc.) (13 patients), pain in the legs (7 patients), fatigue (4 patients), and numb legs (2 patients). Eight patients reached the cone in time, but stopped the test because of numb legs (4 patients), fatigue (3 patients), or pain (1 patient). Four patients completed all 150 shuttles (i.e. 150 10-m courses). Three patients could not walk the first 10 m within the given time limit of less than 12 seconds and scored zero. The reason why one patient stopped the test could not be retrieved.

The FSS scores also varied widely. Of the total study group, 2 patients experienced no fatigue at all (score 1.0) whereas 32 patients reported substantial fatigue (FFS score > 4.0), 4 of them scoring 7.0, the most disabling level of fatigue. Strikingly, the mean score of the test item *fatigue is among my three most disabling symptoms* was 2.47, 4.50, and 4.57 in the MRS subgroups 1, 2, and 3, respectively.

Forty-nine patients scored ≥ 45 points on the BBS, 17 of whom scored 56 points, i.e. optimal balance. The test item *standing on one foot* had the lowest mean score of 2.66 points.

Patients' self-reported autonomy was slightly worse outdoors (median 1.4) than indoors (median 1.0). Only one patient scored more than 2.0 on $IPA_{indoors}$ , whereas 17 patients scored 2.0 or more on $IPA_{outdoors}$ , which means that they experienced significant problems in autonomy outdoors. The $IPA_{indoors}$ item *my chances of getting around in my house where I want to are*... (mean 1.11) and the $IPA_{outdoors}$ item *my chances of going on the sort of trips and holidays I want to go on are*... (mean 1.88) had the worst scores (i.e. highest scores) in the total patient group.

Table 1. Demographic characteristics and functional outcome of 56 patients with chronic idiopathic axonal polyneuropathy.

| | Variable/Instrument | MRS total n=56 (100%) | MRS score 1 n=19 (34%) | MRS score 2 n=30 (54%) | MRS score 3 n=7 (12%) |
|---|---|---|---|---|---|
| Demographics | Age, years | 67.8 | 66.1 | 67.7 | 73 |
| | | (8.6) | (8.4) | (8.9) | (7.1) |
| | Gender (male;female, n) | 45;11 | 15;4 | 25;5 | 5;2 |
| | Disease duration, years | 10.5 | 9 | 11 | 12.6 |
| | | (6.5) | (6.4) | (6.8) | (5.6) |
| Arm functioning | Maximal isometric strength (HHD, z-score) | -0.1 | 0.4 | -0.2 | -0.7 |
| | | (0.9) | (0,7) | (0.8) | (1.1) |
| | Sensory function (SMS, 0-28 points) | 28.0 | 28 | 27.5 | 26 |
| | | (6 to 28) | (26 to 28) | (6 to 28) | (17 to 28) |
| | Pain (n (%)) | 20 | 4 | 13 | 3 |
| | | (36) | (21) | (43) | (43) |
| | Dexterity (SODA, 0-108 points) | 105.0 | 106 | 102 | 96 |
| | | (76 to 108) | (97 to 108) | (82 to 108) | (76 to 108) |
| Leg functioning | Maximal isometric strength (HHD, z-score) | -1.9 | -1.2 | -2.1 | -2.6 |
| | | (1.0) | (0.7) | (0.9) | (0.9) |
| | Sensory function (SMS, 0-28 points) | 15.0 | 16 | 15 | 13 |
| | | (4 to 28) | (9 to 28) | (5 to 22) | (4 to 18) |
| | Pain (n(%)) | 43 | 15 | 24 | 4 |
| | | (77) | (79) | (80) | (57) |
| | Walking perf. (SWT, 0-150 10-m. courses) | 60.4 | 101.0 | 44.9 | 16.3 |
| | | (44.6) | (37.9) | (32.3) | (14.8) |
| | Use of walking aids (n(%)) | 18 | 1 | 11 | 6 |
| | | (32) | (5) | (37) | (86) |
| | Fatigue (FSS, 1-7 points) | 4.5 | 2.7 | 5.2 | 5.3 |
| | | (1 to 7) | (1.0 to 5.4) | (1.7 to 7.0) | (1.6 to 7.0) |
| | Balance (BBS, 0-56 points) | 54.0 | 56 | 54 | 22 |
| | | (13 to 56) | (48 to 56) | (30 to 56) | (13 to 56) |
| | Autonomy indoors (IPA, 0-4 points) | 1.0 | 0 | 1.0 | 1.1 |
| | | (0 to 2.1) | (0 to 1.7) | (0 to 2.1) | (0.6 to 1.9) |
| | Autonomy outdoors (IPA, 0-4 points) | 1.4 | 0.6 | 1.8 | 2.4 |
| | | (0 to 3.4) | (0 to 1.6) | (0 to 2.8) | (1.4 to 3.4) |

Values are mean (SD) or median (range) unless stated otherwise.
HHD, hand-held dynamometry; SMS, sensory modality score; SODA, sequential occupational dexterity assessment; SWT, modified shuttle walk test; FSS, fatigue severity scale; BBS, Berg Balance Scale; IPA, impact on participation and autonomy questionnaire; MRS, Modified Rankin Scale: 0 = no symptoms at all; 1 = no significant disability despite symptoms: able to carry out all usual duties and activities; 2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance; 3 = moderate disability: requiring some help, but able to walk without assistance; 4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance; 5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention.

## Correlation studies

Moderate Pearson correlation coefficients were found between the $IPA_{indoors}$ and $IPA_{outdoors}$ scores on the one hand, and the SWT and FSS scores on the other (Table 2), meaning that patients who reported having good autonomy had a good walking ability and reported almost no fatigue. Strikingly, post-hoc analysis showed a higher correlation between balance and muscle strength of the legs ($r=0.57$ ($p<0.01$)), than between balance and sensory function of the legs ($r=0.01$ (n.s.)). Correlations between muscle strength or sensory function of the legs and fatigue were $r=0.40$ ($p<0.01$) and $r=0.22$ (n.s.), respectively. Analysis of the correlation coefficients revealed no multicollinearity ($r \geq 0.90$).

The results from the hierarchical linear regression analyses (stepwise procedure) for arm functioning are shown in Fig. 2a. Muscle strength and sensory function

together explained almost 30% of the total variance in SODA scores, after adjustment for age. Even less variance was explained by muscle strength and dexterity on one hand, and autonomy indoors on the other (17% and 13%, respectively). With regard to leg functioning (Fig. 2b), 63% of the variance in SWT scores was explained by age, muscle strength and fatigue. Sensory function and fatigue, and balance and fatigue accounted for 46% and 56% of the variance in the $IPA_{indoors}$ and the $IPA_{outdoors}$ scores, respectively, after adjustment for age and the use of walking aids. On the basis of the beta values, fatigue was the main determinant (β=0.504 and β=0.561, respectively). Walking performance explained 42% and 49% of the variance in the $IPA_{indoors}$ and the $IPA_{outdoors}$ scores, respectively. Again, the results were not substantially different after adjustment for age and the use of walking aids. All percentages were significant (p<0.01).

Table 2. Pearson correlation of variables related to of demographic features, arm and leg functioning, fatigue, balance, and autonomy.

| | | SODA | SWT | IPAindoors | IPAoutdoors |
|---|---|---|---|---|---|
| | Age | -0.14 | **-0.53** | 0.25 | **0.36** |
| | Disease duration | -0.24 | **-0.40** | *0.28* | **0.45** |
| Arm functioning | Maximal isometric strength (HHD) | **0.48** | | **-0.42** | |
| | Sensory function (SMS) | **0.41** | | -0.23 | *-0.33* |
| | Pain | -0.22 | | 0.07 | 0.18 |
| | Dexterity (SODA) | | | **-0.35** | |
| Leg functioning | Maximal isometric strength (HHD) | | **0.51** | **-0.42** | **-0.47** |
| | Sensory function (SMS) | | 0.22 | **-0.41** | *-0.31* |
| | Pain | | 0.14 | -0.02 | -0.10 |
| | Walking performance (SWT) | | | **-0.65** | **-0.71** |
| | Walking aids / foot orthoses | | **-0.60** | **0.45** | **0.53** |
| | Fatigue (FSS) | | **-0.53** | **0.62** | **0.64** |
| | Balance (BBS) | | **0.52** | **-0.37** | **-0.50** |

Italics: p<0.05; bold: p<0.01.

HHD, hand-held dynamometry; SMS, sensory modality score; SODA, sequential occupational dexterity assessment; SWT, modified shuttle walk test; FSS, fatigue severity scale; BBS, Berg Balance Scale; IPAindoors, impact on participation and autonomy questionnaire, sub-scale autonomy indoors; IPAoutdoors, impact on participation and autonomy questionnaire, sub-scale autonomy outdoors.

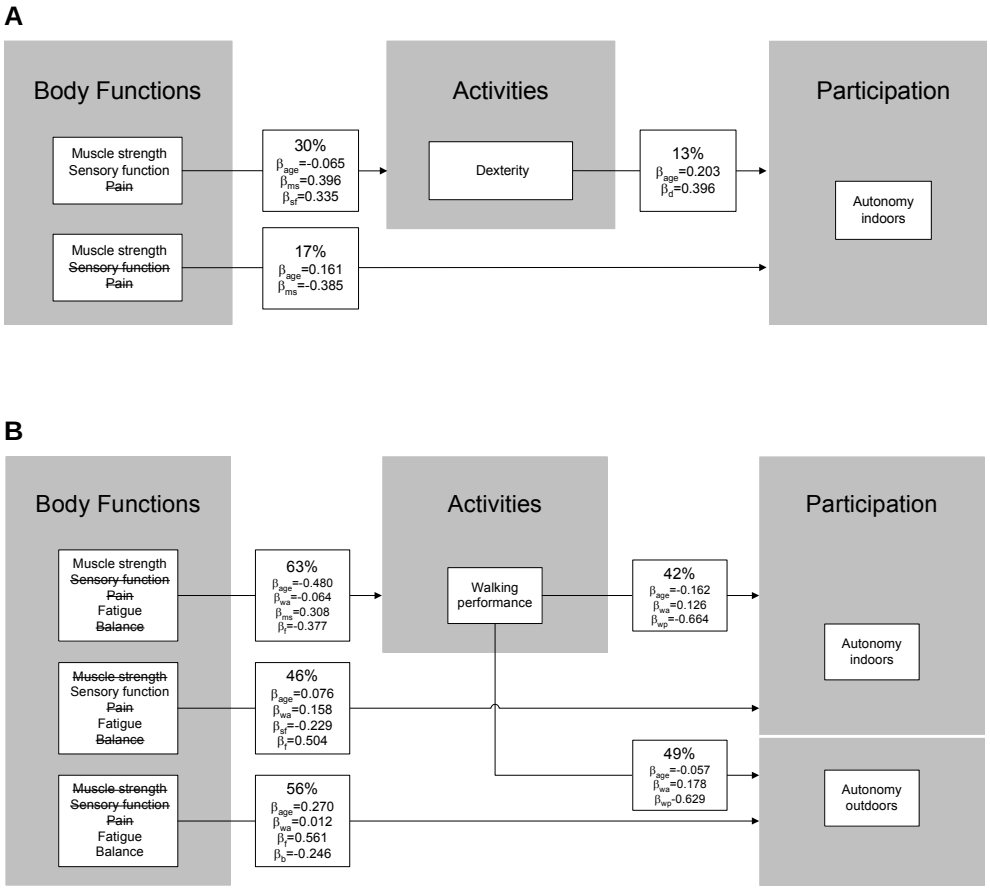


Fig. 2 Linear regression analysis of associations between body functions, activities, and participation, for arm functioning (A) and leg functioning (B), after adjustment for age (A and B) and the use of walking aids (B).

*Interpretation (Fig. 2A, box starting with 30%): analysis of the effect of independent body functions (represented by muscle strength, sensory function, and pain) on dependent activity (represented by dexterity), resulted in a model explaining a total of 30% (Adjusted $R^2$ x100) of the total variance in dexterity scores, when adjusted for age, with a significance of p<0.01. Pain was eliminated as contributing variable in the stepwise procedure. The relative contribution of the independent variables is expressed as β, the standardized coefficient beta. $\beta_{age}$ , beta age; $\beta_{ms}$ , beta muscle strength; $\beta_{sf}$ , beta sensory function; $\beta_{d}$ , beta dexterity; $\beta_{wa}$ , beta walking aids; $\beta_{f}$ , beta fatigue; $\beta_{b}$ , beta balance; $\beta_{wp}$ , beta walking performance. In Fig. 2A, box 30%: when dexterity on the SODA is improved by 1 point, age is increased by -0.065 years, muscle strength is increased by 0.396 Z-score, and sensory function is increased by 0.335 points.*

## DISCUSSION

This is the first detailed study of the functioning of patients with CIAP. Besides known impairments of muscle strength, sensory function, and pain, we showed that fatigue and walking disability markedly interfere with patients' functioning in daily life.

The importance of patients' walking ability is shown by the finding that walking ability explained 42% of the variance in autonomy indoors and 49% of the variance in autonomy outdoors. Moreover, 33 patients mentioned walking as their most limiting activity in daily life, with other activities such as maintaining a standing position (7 patients), transferring (3 patients), manipulations of the hands (1 patient) being mentioned less frequently. Twenty-four patients had serious walking limitations, with SWT scores ≤ 50 and a maximum walking velocity of 4.5 km/h. These values are lower than reference values for maximum walking distance and maximum walking speed in healthy adults[21,31]. In the literature, the validity and reliability of the SWT were based on assessment of endurance in patients with cardiorespiratory failure. In our study, 7 patients stopped the test because of cardiorespiratory failure whereas 44 patients stopped because of neurological symptoms. The 7 patients suffered from chronic heart failure (3 patients) and COPD (2 patients), or had a history of cardiac bypass surgery (2 patients). Eight patients stopped the test because of pain in the legs. These patients did not habitually suffer from intermittent claudication. Muscle strength and fatigue, when adjusted for age and the use of walking aids, explained 63% of the variation in walking ability scores, leaving thus 37% unexplained. This unexplained percentage may be attributed in part to psychological factors such as perceived behaviour control over activities. Recently, Schröder *et al*.[32] showed that such control perceptions explained 9% of the variance in SWT performance in patients with CIAP.

Thirty-two patients reported substantial fatigue. Surprisingly, most of these patients considered their autonomy indoors and outdoors as being quite satisfactory ($IPA_{indoors}$ score <2.0 in 55 patients, $IPA_{outdoors}$ score <2.0 in 39 patients). Fatigue correlated fairly well with patients' walking ability and autonomy, and contributed substantially to the variance in walking ability and perceived autonomy outdoors in all 56 patients. Therefore, next to walking ability, fatigue seems to be important to patient's functioning. A comparable relationship between fatigue and physical functioning has been found in patients with immune-mediated polyneuropathies[23], and in patients with facioscapulohumeral muscular dystrophy, hereditary motor and sensory neuropathy type I, and adult onset myotonic dystrophy[33]. Future studies should determine whether fatigue is a consequence of

axonal degeneration or of the limited walking ability, and whether fatigue can be counteracted by interventions such as exercise training.

The balance test scores were relatively high, which suggests that the patients had only minor problems with balance. However, in our experience patients with CIAP often complain about balance problems during motor performance when there is less visual control (e.g. walking or standing in the dark), or during so-called 'double tasking', which suggests that more demanding tests of balance should be used.

As reported earlier for chronic axonal polyneuropathy, we also found functioning of the arms to be affected less than that of the legs in patients with CIAP. Sensory function and muscle strength explained only 30% of the variation in dexterity scores, which may be because the SODA assesses not only muscle strength related tasks (e.g. *unscrewing a bottle*) but also manipulative tasks (e.g. *buttoning a blouse*). Post-hoc analysis showed that patients had more difficulty with the manipulative tasks. Also, the tasks in general may not have been demanding enough.

Seven patients were classified MRS score 3, which is relatively high compared with the numbers reported in other studies of patients with CIAP[2,16]. As in the other studies, this was probably due to comorbidity. In our tertiary referral center patients are often referred to our outpatient department after previous evaluation by other neurologists. Patients with mild disease are therefore probably less represented, although there are still 19 patients with MRS score 1 included. Overall, sensory function and age seemed less relevant to functioning, which is in accordance with Vrancken *et al*.[34]. Although patients with CIAP do experience sensory dysfunction and pain, their balance, walking ability, and autonomy seem not to be severely influenced by these impairments. Instead, the most relevant parameters were muscle strength, fatigue, and walking ability, all of which may benefit from therapeutic exercise. For example, it has been shown that fatigue and muscle strength improve after bicycle exercise training in patients with inflammatory neuropathy[35]. We believe that future studies should focus on improving the walking ability and balance of patients with CIAP, and on decreasing fatigue by means of functional training. A potential limitation of our study is that the instruments we used were all psychometrically validated in non-CIAP patients. However, the high internal consistency of the BBS, FSS, SODA, and IPA, and the outcome on the SWT, might support the usefulness of these tests in patients with CIAP but need to be validated. Consequently, these clinimetric tools – apart from the BBS – can be recommended for use in both research and clinical settings, in

addition to the MRS, whenever functioning needs to be assessed. However, further investigations are necessary.

In conclusion, strength, fatigue, and walking ability are a problem in patients with CIAP and adversely affect patient autonomy. Patients with CIAP can be classified by means of the frequently used MRS; however, more detailed information about functioning can be obtained with the FSS and the SWT. The instruments used in this study seem to be of clinical relevance, although a more demanding, multitask instrument for balance should be used. Patients with CIAP might benefit from therapeutic exercise. Future studies, preferably with a longitudinal design, should shed light on the determinants of functioning in these patients and evaluate potential interventions.

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# 5

# FUNCTIONING OF PATIENTS WITH MULTIFOCAL MOTOR NEUROPATHY

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**ABSTRACT**

Patients with multifocal motor neuropathy (MMN) have slowly progressive, predominantly distal asymmetric limb weakness without sensory loss. While previous studies have investigated the impact of MMN on body functions and structures, relatively little is known about the impact of patients' weakness on daily functioning. The aim of the present cross-sectional study, involving 47 patients with MMN, was to evaluate determinants of patients' functioning. Most patients showed not only muscle weakness but also fatigue, limited dexterity, and limited walking ability. Regression models showed that age, hand aids, and muscle strength scores together explained 54% of the variance in dexterity scores, which in turn explained 8% of the variance in patients' scores for autonomy indoors. Age, the use of walking aids, and muscle strength scores together explained 58% of the variance in walking ability scores, which in turn explained 18% of the variance in patients' scores for autonomy indoors and 7% of the variance in patients' scores for autonomy outdoors. Assessment of determinants of patient functioning may make it possible to tailor interventions to address these aspects and thereby improve patients' functioning in daily life.

## INTRODUCTION

Multifocal motor neuropathy (MMN) is a chronic immune-mediated disorder characterized by slowly progressive, predominantly distal, asymmetric limb weakness in the arms more than the legs, not accompanied by sensory loss. The mean age of onset is 40 years, with a male predominance. Patients with MMN respond to treatment with high-dose intravenous immunoglobulin (IVIg) [1].

Previous studies of patients with MMN have mainly focused on body functions and structures, using neurological, electrophysiological, or laboratory assessments. However, patients with MMN report not only weakness but also serious problems in overall functioning, and specifically in activity limitations[2,3]. According to the International Classification of Functioning, Disability, and Health (ICF) of the World Health Organization*, functioning* encompasses the interactions of all *body functions and structures* (e.g. muscle strength), *activities* (e.g. walking ability), and social *participation*, taking into account personal (e.g. gender, age) as well as environmental factors (e.g. walking aids)[4]. Several investigators have mentioned the need for appropriate instruments to assess arm and leg functioning in patients with acute and chronic immune-mediated neuropathies[3,5,6], because knowledge of the broader functioning of these patients may make it possible to tailor interventions, thereby improving the daily life functioning of patients[3,6].

The aim of the present cross-sectional study was to evaluate the determinants of patients' functioning in terms of the ICF classification.

## MATERIALS AND METHODS

### Patients

The functioning of the 47 patients with clinically stable MMN[7] was evaluated in a cross-sectional study between March and November 2007. Thirty-five patients received intermittent IVIg, and the remaining 12 patients did not receive pharmacotherapy. The study was approved by the ethics committee of the University Medical Center Utrecht.

### Design

All measurements were performed by one examiner (PGE), who has more than 10 years of clinical experience with such patients and with the instruments used. Demographic data were recorded and patients were classified into subgroups using the Modified Rankin Scale[8]. The functioning of the arms and legs (maximal isometric muscle strength, dexterity, walking ability), the use of hand and walking aids (yes/no), patients' self-reported fatigue, and self-reported autonomy indoors

and outdoors were evaluated, using instruments that tapped patients' perceptions of their problems[2,3] and those recommended by the Inflammatory Neuropathy Cause and Treatment (INCAT) Group[6,9], and consistent with the ICF. All assessments were done in a quiet and comfortable room at our outpatient clinic, except for walking performance, which was assessed in the gymnasium of the outpatient clinic. Questionnaires were sent to the patients, who were asked to complete them the day before they came to the clinic for the assessments. Questionnaire information was checked in the presence of the patients.

**Measurements**

*Maximal isometric strength*

The maximal isometric strength of the muscles of the arms and legs was measured bilaterally using a MicroFET® hand-held dynamometer (Hoggan Health Industries Inc., Draper, Utah, USA). A Jamar® dynamometer (Therapeutic Equipment Co., Clifton, New Jersey, USA) was used to measure handgrip strength. The reliability and validity of measurements made with these instruments are good[10-12]. Muscle strength was measured twice on each side using the 'make' test of the shoulder abductors, the elbow flexors, the wrist extensors, the hip abductors, the knee extensors, and the ankle dorsal flexors, bilaterally, according to Andrews *et al*.[13]. Handgrip strength was measured twice on each side, according to Mathiowetz *et al*.[14]. The highest score for each measurement was recorded.

*Fatigue*

Fatigue is a major impairment in patients with immune-mediated polyneuropathies[9]. We measured self-reported fatigue using the validated Dutch version of the Fatigue Severity Scale (FSS)[15]. The FSS is a brief nine-item self-report questionnaire with answers ranging from 1 ('strongly disagree') to 7 ('strongly agree') for each item. The mean score for the nine items ranges from 1 ('no signs of fatigue') to 7 ('most disabling fatigue') and the normative value is 2.3 points in healthy adults[15]. A score higher than 5.0 is indicative of severe fatigue[9]. The FSS possesses good psychometric properties in patients with inflammatory polyneuropathies[9].

*Dexterity*

In line with the nature of the dexterity limitations in patients with MMN[2,3], we selected a bimanual dexterity test, the Sequential Occupational Dexterity Assessment (SODA). The SODA is a reliable and valid performance-based test[16] in which dexterity is measured in 12 standardized tasks, such as writing, cutlery use,

and picking up coins. These tasks assess the function of relevant handgrips, such as pinch grip and key grip. Eighteen items are scored, with scores ranging from 0 (unable to perform the task) to 6 (able to perform the standardized task without difficulty). The range of scores on the SODA is thus 0 to 108.

Hand functioning was also assessed with the nine-hole peg test[17]. This test is valid and reliable in patients with inflammatory polyneuropathies[6]. An average time score was calculated as the mean of six assessments, three for the left hand and three for the right hand.

*Walking ability*

Patients with MMN often find it difficult to walk long distances, and because these patients tend to show ceiling effects on the 10-Meter Walk Test[3], walking ability was assessed with a modified incremental Shuttle Walk Test[18]. Patients were asked to walk around a 10-m course marked by two cones placed 9 m apart, with 0.5 m allowed for turning at each end. Walking speed was regulated by prerecorded metronomic signals. The patients were asked to turn at the cones at each signal. The initial walking speed was 3 km/hour but was increased by 0.5 km/hour every 2 minutes; the maximum walking speed was 7.0 km/hour. Standard instructions were given before the test, and respondents were encouraged to walk as long as they could without risking falling, overuse, or pain. The use of walking aids was permitted. The number of shuttles (i.e. 10-m courses) was recorded on test completion (150 times the 10-m course) and when the test was stopped because the patient reported severe symptoms (e.g., pain or fatigue) or could no longer complete the 10-m course (the subject was not within 0.5 m of the cone at the prerecorded signal). Higher numbers indicate better performance on the test, with a maximum of 1500 m. If the patients did not complete the test, they were asked why they had stopped. The Shuttle Walk Test is a reliable, valid, and responsive test in various patient populations[19,20]. It has recently been validated in patients with MMN and chronic idiopathic axonal polyneuropathy[21].

*Autonomy*

The Impact on Participation and Autonomy (IPA) is a generic, reliable, and valid self-assessment questionnaire[22-24] that measures perceived participation and autonomy in social life. It contains five subscales with 31 items. Each item is graded on a 5-point rating scale with discrete responses, ranging from 0 (very good) to 4 (very poor). Each subscale is scored separately and is expressed in relative scores, with lower scores representing greater participation and autonomy.

We used the autonomy indoors ($IPA_{indoors}$) and autonomy outdoors ($IPA_{outdoors}$) subscales because these scales include items related to self-care, indoor mobility, the frequency of social contacts, leisure, and outdoor mobility, items that depend to a large extent on the individuals' general functional mobility.

**Data analysis**

Functioning was assessed using descriptive statistics. Scores were calculated for the whole group and subgroups determined by the Rankin scores. We calculated mean muscle strength Z-scores, using reference values for healthy adults[14,25], for the arms (Z-scores for shoulders, elbows, wrists, and handgrip), and the legs (Z-scores for hips, knees, and ankles). The internal consistency of the FSS, SODA dexterity test, and $IPA_{indoors}$ and $IPA_{outdoors}$ was assessed.

We analyzed the associations between determinants in two consecutive steps. The first step involved analyzing correlations (Pearson's r) between single body functions, activities, and participation outcome measures, as well as personal and environmental factors. Correlation outcome scores were interpreted as 'very weak', 'low', 'moderate', 'good', or 'very strong'[26]. This was followed by hierarchical multiple univariate linear regression analysis (stepwise procedure) to investigate which body functions (muscle strength and fatigue) best explained the variance in activity scores (walking ability and dexterity) and participation (autonomy), as well as which activities best explained the variance in participation scores. We adjusted for age and the use of hand and walking aids. The strength of the association between the dependent variable and the independent variables is expressed as a percentage (adjusted $R^2$ x 100), and the relative importance of the independent variables is given as a standardized coefficient beta. Analyses were performed using the Statistical Package for Social Sciences (version 11.5). All tests were two-sided and P values < 0.05 were considered significant.

**RESULTS**

Demographic characteristics and functional outcome measures of all participants are presented in Table 1. Of the patients who received IVIg, 4 were in Rankin subgroup 1, 24 in subgroup 2, and 7 in subgroup 3. The internal consistency of the FSS, SODA, and $IPA_{indoors}$ and $IPA_{outdoors}$ in this study was good (Cronbach's α: 0.95, 0.95, 0.92, and 0.90 respectively). Twenty-three patients mentioned reduced dexterity as the most limiting problem in daily life, followed by reduced walking ability (15 patients), and general heavy work such as household chores or sports (8

patients). One patient reported few signs and did not experience any activity problems.

### Functional outcome measures

Forty-four patients had problems with dexterity (SODA scores ranging from 21 to 104 points); the remaining 3 patients had an optimal score of 108 points. The patients experienced the most difficulty (lowest SODA scores) with using a knife and spoon, buttoning a shirt, and pouring water from a can into a glass.

Table 1. Demographic characteristics and functional outcome of 47 patients with multifocal motor neuropathy.

| | Variable/Instrument | MRS total n=47 (100%) | MRS score 1 n=7 (15%) | MRS score 2 n=30 (64%) | MRS score 3 n=10 (21%) |
|---|---|---|---|---|---|
| Demographics | Age, years | 51.9 (11.1) | 46.9 (10.8) | 51.3 (10.9) | 56.9 (10.9) |
| | Gender (male;female, n) | 33;14 | 5;2 | 23;7 | 5;5 |
| | Disease duration, years | 13.7 (8.7) | 12.6 (5.3) | 12.9 (8.3) | 17.1 (11.5) |
| | Number of patients with impaired functions of: | | | | |
| | right hand; left hand; both hands | 6;12;27 | 1;4;1 | 5;8;16 | 0;0;10 |
| | right leg; left leg; both legs | 5;14;14 | 0;1;1 | 5;9;8 | 0;4;4 |
| | Immunoglobulin dosage (g/week) | 13.9 (5.6) | 12.1 (2.7) | 13.2 (5.0) | 17.0 (7.9) |
| Arm functioning | Maximal isometric strength (HHD, z-score) | -1.4 (1.1) | -0.3 (1.1) | -1.5 (1.0) | -1.9 (1.1) |
| | Dexterity (SODA, 0-108 points) | 83 (21 to 108) | 103 (82 to 108) | 78 (21 to 104) | 61.5 (24 to 104) |
| | Dexterity (NHP left and right hand, sec) | 26.3 (16.7 to 80.2) | 19.3 16.7 to 26.7) | 26.6 (16.9 to 73.4) | 33.5 17.8 to 80.2) |
| | Use of hand aids (n(%)) | 5 (11) | 0 (0) | 2 (7) | 3 (30) |
| Leg functioning | Maximal isometric strength (HHD, z-score) | -1.5 (1.1) | -0.4 (1.1) | -1.4 (0.9) | -2.3 (1.2) |
| | Walking perf. (SWT, 0-150 10-m. courses) | 89.6 (42.2) | 128.7 (29.4) | 92.8 (37.4) | 52.9 (36.0) |
| | Use of walking aids (n(%)) | 11 (23) | 0 (0) | 6 (20) | 5 (50) |
| | Fatigue (FSS, 1-7 points) | 5.3 (1.4 to 7.0) | 4.2 (1.7 to 5.6) | 5.0 (1.4 to 6.9) | 6.1 (2.3 to 7.0) |
| | Autonomy indoors (IPA, 0-4 points) | 0.7 (0 to 2.1) | 0 (0 to 1.0) | 0.5 (0 to 1.6) | 1.0 (0.4 to 2.1) |
| | Autonomy outdoors (IPA, 0-4 points) | 1.0 (0 to 3.8) | 0 (0 to 1.0) | 1.0 (0 to 2.4) | 1.7 (1.0 to 3.8) |

Values are means (SD) or medians (range) unless stated otherwise.
HHD, hand-held dynamometry; SODA, sequential occupational dexterity assessment; NHP, nine-hole peg test; SWT, modified shuttle walk test; FSS, fatigue severity scale; IPA, impact on participation and autonomy questionnaire; MRS, Modified Rankin Scale: 0 = no symptoms at all; 1 = no significant disability despite symptoms: able to carry out all usual duties and activities; 2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance; 3 = moderate disability: requiring some help, but able to walk without assistance; 4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance; 5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention.

The mean scores on the Shuttle Walk Test varied widely across the Rankin subgroups. Various reasons were given for stopping the test: 35 patients were unable to reach the last cone in time, because [A] their legs ‘blocked’ (i.e. they could not move their legs any faster, but did not experience this as a natural transition to running) (24 patients; maximum walking speed range 3.0-7.0 km/h), [B] they could not walk any faster and started to run, which is not permitted in the

test (6 patients; maximum walking speed range 6.0-7.0 km/h), [C] their legs were tired (3 patients; maximum walking speed range 4.0-5.5 km/h), and [D] they experienced fatigue (i.e. lack of endurance) or cramps (2 patients; maximum walking speed 6.5 km/h). Six patients reached the cone in time, but stopped the test because they stumbled (3 patients; maximum walking speed range 3.5-5.5 km/h), their legs 'blocked' (2 patients; maximum walking speed 6.5 km/h), or had tired legs (1 patient; maximum walking speed 5.5 km/h). Six patients completed all 150 shuttles (i.e., they walked 1500 m at a final speed of 7.0 km/h). The most frequently used walking aids were ankle-foot orthoses and/or orthopaedic shoes (n=10).

The severity of fatigue varied considerably across the Rankin subgroups. Most patients (n=25) reported severe fatigue (FSS score ≥5.0), but 3 experienced no fatigue (mean score range 1.0-2.0). Patients' self-reported autonomy was slightly worse outdoors (median 1.1) than indoors (median 0.7). Only one patient reported frequently experiencing problems with autonomy indoors ($IPA_{indoors}$ >2.0), whereas eight patients reported frequently experiencing such problems outdoors ($IPA_{outdoors}$ ≥2.0).

**Correlation studies**

Isometric arm strength was highly correlated with the SODA dexterity scores (r=0.71) (Table 2), so that patients whose manual dexterity was good also had good isometric strength in their arms. In contrast, leg muscle strength was poorly correlated with walking ability in the Shuttle Walk Test (r=0.35). There were weak to moderate correlations between the SODA dexterity scores and the Shuttle scores on the one hand and the $IPA_{indoors}$ and $IPA_{outdoors}$ scores on the other (range r=-0.29 to r=-0.46). The correlation between the FSS scores and $IPA_{outdoors}$ scores was moderate (r=0.62), so that patients who experienced higher levels of fatigue had a lower perceived autonomy outdoors.

Table 2. Pearson correlation coefficients for demographic characteristics and functioning.

| | | SODA | SWT | IPAindoors | IPAoutdoors |
|---|---|---|---|---|---|
| | Age | **-0.48** | **-0.66** | *0.29* | 0.04 |
| | Disease duration | *-0.36* | **-0.43** | 0.17 | 0.03 |
| Arm functioning | Maximal isometric strength (HHD) | **0.71** | | *-0.30* | |
| | Dexterity (SODA) | | | *-0.34* | |
| | Dexterity (NHP) | **-0.81** | | | |
| | Hand aids / hand orthoses | -0.01 | | 0.01 | |
| Leg functioning | Maximal isometric strength (HHD) | | *0.35* | -0.28 | *-0.37* |
| | Walking performance (SWT) | | | **-0.46** | *-0.29* |
| | Walking aids / foot orthoses | | **-0.44** | 0.07 | 0.12 |
| | Fatigue (FSS) | | -0.22 | *0.34* | **0.62** |

Italics: p<0.05; bold: p<0.01.

HHD, hand-held dynamometry; SODA, sequential occupational dexterity assessment; NHP, nine-hole peg test; SWT, modified shuttle walk test; FSS, fatigue severity scale; IPAindoors, impact on participation and autonomy questionnaire, sub-scale autonomy indoors; IPAoutdoors, impact on participation and autonomy questionnaire, sub-scale autonomy outdoors.

The results of the hierarchical linear regression analyses (stepwise procedure) for arm functioning are shown in Fig. 1A. Muscle strength together with age and the use of hand aids explained 54% of the total variance in SODA dexterity scores. On the basis of the beta values, muscle strength was the main determinant (β=0.63). Far less variance was explained by muscle strength and dexterity on the one hand and autonomy indoors on the other (7% and 8%, respectively). As regards leg functioning (Fig. 1B), 58% of the variance in Shuttle scores was explained by age, the use of walking aids, and muscle strength, the main determinant being age (β=-0.64). Fatigue accounted for 14% and 36% of the variance in the $IPA_{indoors}$ and the $IPA_{outdoors}$ scores, respectively, after adjustment for age and the use of walking aids. Walking performance explained 18% and 7% of the variance in the $IPA_{indoors}$ and the $IPA_{outdoors}$ scores, respectively. All percentages were significant (p<0.01).

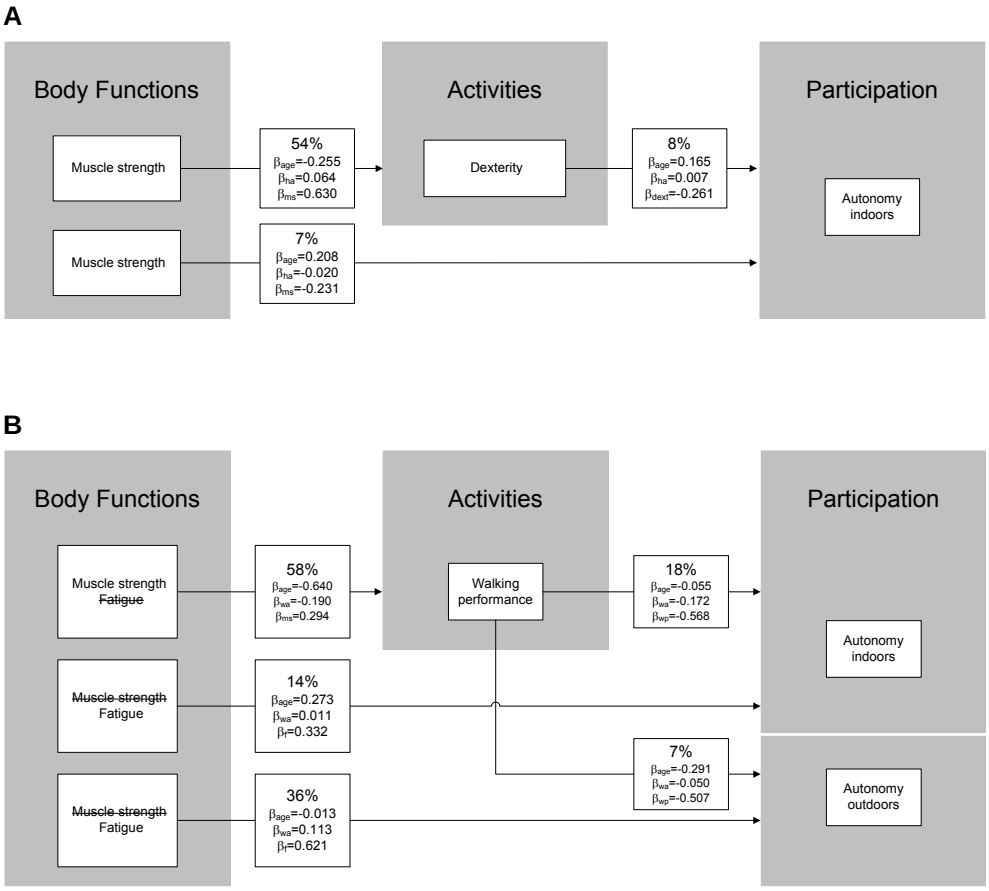


Fig. 1 Linear regression analysis of associations between body functions, activities, and participation, for arm functioning (A) and leg functioning (B), after adjustment for age (A and B), the use of hand aids (A), and the use of walking aids (B).

*Interpretation (Fig. 1A, box headed '54%'): analysis of the effect of independent body function (represented by muscle strength) on dependent activity (represented by dexterity (SODA)) resulted in a model explaining a total of 54% (adjusted $R^2$ x100) of the total variance in dexterity scores, when adjusted for age and the use of hand aids, with a significance of p<0.01. The relative contribution of the independent variables is expressed as β, the standardized coefficient beta. $\beta_{age}$, beta for age; $\beta_{ha}$, beta for hand aids; $\beta_{ms}$, beta for muscle strength; $\beta_{dext}$, beta for dexterity (SODA); $\beta_{wa}$, beta for walking aids; $\beta_{f}$, beta for fatigue; $\beta_{wp}$, beta for walking performance. In Fig. 1A, box headed 54%: an age increase of 0.255 years corresponds to an improvement on the SODA by 1 point.*

## DISCUSSION

This study assessed the functioning of 47 patients with MMN. Although dexterity and walking ability were affected in most patients, their perceived autonomy indoors and outdoors was not seriously affected, and autonomy was not closely associated with their dexterity and walking ability.

Patients with MMN experience impaired or restricted dexterity as a major problem[2,3]. In this study, SODA dexterity test scores were strongly correlated with muscle strength scores, explaining 54% of the variance. The unexplained variance may be attributed to poor hand coordination. A post-hoc analysis showed that the nine-hole peg dexterity scores explained 40% of the variance in muscle strength scores. The low correlation between autonomy indoors and SODA dexterity ($r \leq 0.40$) suggests that other factors also influence patients' autonomy indoors, such as psychological factors[27], or that patients find alternative motor solutions for specific problematic activities, but this remains to be confirmed by further research. As the SODA and nine-hole peg test scores were highly correlated ($r=-0.81$), we recommend using the nine-hole peg test in clinical practice, with the SODA being used when a more comprehensive assessment of patients' dexterity is required. The median SODA score of patients with chronic idiopathic axonal polyneuropathy[28] was higher than that of the patients in this study (105 versus 83), indicating that patients with MMN have more problems with dexterity than do patients with idiopathic polyneuropathy. Moreover, muscle strength scores and sensory function scores together explained only 30% of the variance in the SODA scores in the patients with chronic idiopathic axonal polyneuropathy, whereas muscle strength alone explained 54% of the variance in the current patients with MMN.

Many patients experienced limitations in their walking ability, evaluated with the Shuttle Walk Test. Seven (15%) patients had a severe walking disability with Shuttle scores ≤ 50 and an accompanying maximum walking velocity of 4.5 km/h. These values are lower than the reference values for maximum walking distance and maximum walking speed in healthy adults[29,30]. The Shuttle Walk Test was originally developed to assess the functional capacity of patients with cardiorespiratory failure. In our study, only 1 patient stopped the test because of an impaired functional capacity, whereas 33 patients were forced to stop because of symptoms that seemed to be directly related to their polyneuropathy. Comorbidity did not directly influence test results. Muscle strength, age, and walking aids explained 58% of the variance in Shuttle scores, similar to findings in patients with idiopathic polyneuropathy[28]. The unexplained variance may be caused by endurance and/or coordination deficits in the legs. The Shuttle scores explained

only 18% and 7% of the variance in the scores for autonomy indoors and outdoors, which is lower than the 42% and 49% found in patients with idiopathic polyneuropathy[28]. Post-hoc analysis of Cook' distance showed that this discrepancy was not because of outliers, and scatterplots showed no linear or non-linear relationship between the Shuttle scores and the IPA scores.

Many patients reported experiencing severe fatigue, which adversely affected their autonomy outdoors, as evidenced by the modest correlation between FSS and $IPA_{outdoors}$ scores and the substantial contribution of fatigue to the explained variance in patients' autonomy outdoors. Fatigue has previously been found to be an important determinant in other neuromuscular disorders[9,28,31]. This makes it worthwhile to investigate the nature of fatigue and whether it is amenable to medical intervention or exercise training, as previously shown for the Guillain-Barré syndrome[32].

Lastly, the internal consistency of the FSS, SODA, and IPA was high. Thus, these tests might prove useful for evaluating the functional health of patients with MMN. This would require evaluation of the clinimetric properties of these instruments. Moreover, because these instruments have non-linear outcome measures, it would be advantageous if linear weighting could be applied, as done recently for the FSS for other immune-mediated disorders[33].

In conclusion, strength, fatigue, dexterity, and walking ability are relevant determinants in the functioning of patients with MMN, but seem to have only a limited influence on patients' autonomy. The SODA and the Shuttle Walk Test proved useful for investigating determinants of patients' functioning, knowledge which will help clinicians to tailor interventions.

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# 6

# PAIN IN PATIENTS WITH CHRONIC IDIOPATHIC AXONAL POLYNEUROPATHY

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**ABSTRACT**

Pain in patients with chronic idiopathic axonal polyneuropathy (CIAP) has never been studied in detail. The aim of the study was to investigate the pain experienced by patients with CIAP, and to determine whether pain is associated with health-related quality of life (HRQoL). The McGill Pain Questionnaire (MPQ) and the RAND-36 were used in a cross-sectional study. Sixty-three of 91 patients with CIAP reported experiencing pain, describing it as nagging (56%) and annoying (52%). Of these patients, 27 were classified in a subgroup with neuropathic pain (median VAS = 33 mm), 25 in a subgroup with non-neuropathic pain (median VAS = 34 mm), and 11 in a mixed-pain subgroup (median VAS = 25 mm). Non-neuropathic pain was as common and as painful as neuropathic pain. Pain was strongly associated with the physical functioning domain of the RAND-36 in patients in the mixed pain subgroup ($r=-0.71$, $p< 0.05$). Neuropathic and non-neuropathic pain syndromes should be distinguished in patients with CIAP who experience pain, to enable appropriate tailoring of treatment.

## INTRODUCTION

Patients with chronic idiopathic axonal polyneuropathy (CIAP) suffer from slowly progressive distal symmetric sensory or sensory motor impairments and frequently experience pain, but the underlying cause of the polyneuropathy has not been established[1-3]. Although pain is recognized as an important impairment in CIAP[3], the prevalence and nature of this pain and its association with health-related quality of life (HRQoL) have never been studied in detail. Since CIAP and non-neuropathic pain frequently occur in elderly people[2,4], and the treatment of non-neuropathic pain differs from that of neuropathic pain, it is important to study the pain characteristics of these patients.

Several instruments have been developed to assess the presence and severity of pain, including the McGill Pain Questionnaire (MPQ)[5-9] and newly developed tools such as the Neuropathic Pain Scale (NPS)[10] and the Douleur Neuropatique 4 Questions (DN4)[11]. To date, no studies have distinguished between neuropathic and non-neuropathic pain in patients with CIAP. A recent review of the consequences of peripheral and central neuropathic pain on patients' HRQoL found the presence and severity of neuropathic pain to be associated with a lower reported HRQoL in the domains of physical and emotional functioning, sleep, role functioning, and global quality of life[12]. Hughes *et al*.[3] found that patients with CIAP and neuropathic pain had a poorer quality of life (in terms of all SF-36 domains) than healthy controls, but they scored pain dichotomously. The aims of the present study were to determine the prevalence and characteristics of the pain experienced by patients with CIAP and whether pain is associated with HRQoL.

## MATERIALS AND METHODS

Ninety-one patients diagnosed with CIAP who visited the outpatient clinic of the Department of Neuromuscular Diseases of the University Medical Center Utrecht, the Netherlands, between 2003 and 2008 participated in the study. As reported by McLeod *et al*.[1], Notermans *et al*.[2], and Hughes *et al*.[3], CIAP was diagnosed if patients had a slowly progressive distal symmetric sensory or sensorimotor polyneuropathy on neurological clinical examination, and axonal degeneration on neurophysiological examination. Laboratory investigations revealed normal values for hemoglobulin, hematocit, leukocytes, platelets, erythrocyte sedimentation rate, serum glucose, renal function and electrolytes, liver enzymes, serum calcium and phosphorosus, creatinine kinase, serum protein, transketolase, vitamin B1, B6 and B12, thyroid function, immunoelectrophoresis, antinuclear antibodies, cryoglobulin, rheumatoid factors. All patients had undergone a routine chest X-ray. Patients'

functioning was assessed by means of self-rated pain and HRQoL questionnaires. The Ethics Committee of the UMC Utrecht approved the use of the clinical data for publication.

**Measurements**

*Pain*

The McGill Pain Questionnaire (MPQ) measures pain as a multidimensional variable and assesses both quantitative and qualitative aspects of perceived pain. The questionnaire is widely used for both acute and chronic medical conditions[13,14]. The validated Dutch version of the MPQ (MPQ-DLV) was used[15]. The MPQ-DLV comprises four parts: [A] a body chart on which patients indicate painful regions, [B] general questions regarding pain development and current pain status, [C] three visual analogue scales (VAS) reflecting the current ($VAS_{now}$), minimum ($VAS_{min}$) and maximum ($VAS_{max}$) pain scores (a score of 0 mm means no pain, whereas 100 mm represents maximum pain), and [D] 20 sets of three or four adjectives, each describing different qualitative aspects of the perceived pain. For each set of adjectives, the patient may indicate one adjective that best describes his/her pain. Each set of adjectives has a hierarchical construct, with each adjective having its specific pre-determined 'pain-intensity score' ranging from 0 (no pain) to 10 (extreme pain). This allows the adjectives within and between different sets to be compared[16,17].

*Health-related quality of life*

The RAND-36 is a generic multidimensional questionnaire to assess HRQoL and is equivalent to the MOS Short Form-36[18]. It comprises eight domains: *physical functioning*, *social functioning*, *role limitations due to physical problems*, *role limitations due to emotional problems*, *pain*, *mental health*, *vitality,* and *general health perception*. The item scores for each domain are coded, summed, and transformed into a scale ranging from 0 to 100, where 100 is the best possible rating. We used the validated Dutch version of the RAND-36[19,20].

**Methods**

*Classification and analysis of pain*

Three independent raters (NCN, LLT, EL; two neurologists and one physician specializing in rehabilitation medicine, all of whom have clinical and research experience in CIAP) assessed the presence of pain in 91 patients with CIAP. Pain was presumed to be present whenever painful regions were indicated on the MPQ-DLV body chart. Pain was considered not present ('no pain') if the MPQ-DLV

questionnaire had not been completed or if the patient reported experiencing only cramp, tingling, or pricking. On the basis of the MPQ-DLV responses regarding the painful areas marked on the body chart, the $VAS_{now}$, $VAS_{min}$, and $VAS_{max}$ pain scores, the adjectives used to describe the pain experienced, and the answers to the remaining questions, the raters classified the patients with pain into three subgroups: 'neuropathic pain' subgroup (NP), 'non-neuropathic pain' subgroup (NNP), and 'neuropathic as well as non-neuropathic pain' subgroup (NP&NNP). Symmetric distal pain in the feet and/or lower legs, possibly also in the hands and/or lower arms, as reported on the body chart of the MPQ-DLV, was considered to be neuropathic pain. Pain in all other parts of the body and asymmetric pain were considered non-neuropathic pain. In the first instance, the raters, who were blind to patient characteristics, classified 10 randomly chosen patients into one of the three pain subgroups. The inter-rater agreement in classification was substantial (Fleiss' $\kappa = 0.75$)[21], and so the raters classified all the patients with pain into a pain subgroup (Fleiss' $\kappa = 0.64$). If there was disagreement about classification (which was the case for 29 patients), consensus was sought by means of an iterative process. If consensus was still not reached (which was the case for 4 patients), the majority classification was accepted.

*Data analysis*

The internal consistency (Cronbach's α) of the MPQ-DLV and RAND-36 was assessed to determine the internal validity of the instruments used. Descriptive statistics were calculated for the whole group and for the three pain subgroups.

The Spearman rank correlations between the $VAS_{now}$ scores and the individual RAND-36 domain scores were calculated for the patients with and without pain, and for the different pain subgroups, to determine the association between pain and HRQoL. Analyses were performed using the Statistical Package for Social Sciences (version 12.0); $p < 0.05$ was considered significant.

## RESULTS

The internal consistency of the data collected with the three VAS scores of the MPQ-DLV and with the RAND-36 scales was good[22], with Cronbach's α of 0.87 and 0.85, respectively. Tables 1-4 present demographic characteristics and outcome measures of the two questionnaires for the patients with and without pain, as well as for the pain subgroups.

**Pain**

Of the 91 patients with CIAP, 63 (69%) reported pain, which had a median duration of 4.25 years (range, 0–35 years). The median current pain severity on the VAS was 33 mm, with a median minimal pain severity of 16 mm and median maximum pain severity of 63 mm; there was considerable variation in the pain scores (Table 1). In total, 12 patients were classified as having severe pain (VAS score >54 mm), 22 moderate pain (VAS score 30–54 mm), and 29 mild pain (VAS score <30)[23,24]. Sixty-four percent of the patients reported pain of varying severity and 22% reported pain of constant severity; 14% reported experiencing intermittent pain. Thirty-nine percent of patients reported exacerbation of pain at night and 27%

Table 1. Demographic characteristics and MPQ-DLV and RAND-36 outcome scores of 91 patients with chronic idiopathic axonal polyneuropathy.

| | | Study group n=91 (100%) | No pain n=28 (31%) | Pain n=63 (69%) |
|---|---|---|---|---|
| Demographics | Age, years | 67.0 | 67.6 | 66.7 |
| | | (8.9) | (7.7) | (9.4) |
| | Gender (male;female), n | 71;20 | 25;3 | 46;17 |
| | Disease duration, years | 7 | 7.5 | 7 |
| | | (1-25) | (1-20) | (1-25) |
| MPQ-DLV | Pain duration, years | | | 4.25 |
| | | | | (0-35) |
| | Changes in pain over time n(%) | | | |
| | constant severity | | | 14(22) |
| | varying severity | | | 40(64) |
| | intermittent | | | 9(14) |
| | $VAS_{now}$, mm | | | 33 |
| | | | | (0-70) |
| | $VAS_{min}$, mm | | | 16 |
| | | | | (0-69) |
| | $VAS_{max}$, mm | | | 63 |
| | | | | (21-100) |
| RAND-36 | Physical functioning | 50 | 55 | 45 |
| | | (10-100) | (10-100) | (10-95) |
| | Social functioning | 75 | 87.5 | 75 |
| | | (13-100) | (38-100) | (13-100) |
| | Role limitations physical | 50 | 75 | 50 |
| | | (0-100) | (0-100) | (0-100) |
| | Role limitations emotional | 100 | 100 | 100 |
| | | (0-100) | (0-100) | (0-100) |
| | Mental health | 80 | 86 | 76 |
| | | (28-100) | (60-100) | (28-100) |
| | Vitality | 60 | 70 | 60 |
| | | (15-95) | (35-95) | (15-95) |
| | Pain | 67 | 79.5 | 57 |
| | | (0-100) | (45-100) | (0-90) |
| | General health perception | 55 | 60 | 50 |
| | | (0-90) | (25-80) | (0-90) |

Values are mean (SD) or median (range) unless stated otherwise.

reported that physical activities of daily living exacerbated the pain intensity. Twenty-nine percent of the patients were substantially impeded in their leisure activities, sports, or hobbies (i.e. scoring 3 [considerably] or 4 [severe] on the 4-point Likert scale of the MPQ-DLV). The patients used a total of 554 adjectives to describe their pain. Only 133 of these adjectives had a pain intensity score of more than 6.0. The five most-often used pain adjectives had pain intensity scores ranging from 3.9 to 5.5 (Table 2). The most frequently chosen adjective was *nagging* (56%).

Table 2. The five most frequently used pain adjectives and the associated mean pain intensity scores.

| | Adjectives | n (%) | Pain intensity score 0 (non) - 10 (extreme) |
|---|---|---|---|
| Pain, n=63 | nagging (zeurend) | 35(56) | 5.5 |
| | annoying (hinderlijk) | 33(52) | 4.4 |
| | tiring (vermoeiend) | 30(48) | 4.7 |
| | tingling (tintelend) | 29(46) | 3.9 |
| | *awkward (vervelend)* | 26(41) | 4.4 |
| Neuropathic pain, n=27 | nagging (zeurend) | 16 (59) | 5.5 |
| | annoying (hinderlijk) | 14 (52) | 4.4 |
| | tiring (vermoeiend) | 13(48) | 4.7 |
| | *awkward (vervelend)* | 13(48) | 4.4 |
| | tingling (tintelend) | 13(48) | 3.9 |
| Non-neuropathic pain, n=25 | *awkward (vervelend)* | 16 (64) | 4.4 |
| | annoying (hinderlijk) | 12 (48) | 4.4 |
| | nagging (zeurend) | 12 (48) | 5.5 |
| | tingling (tintelend) | 11 (44) | 3.9 |
| | taut (strak) | 10 (40) | 4.8 |
| Neuropathic pain and | tiring (vermoeiend) | 8(73) | 4.7 |
| Non-neuropathic pain, n=11 | annoying (hinderlijk) | 7(64) | 4.4 |
| | nagging (zeurend) | 7(64) | 5.5 |
| | *awkward (vervelend)* | 7(64) | 4.4 |
| | *depressing (deprimerend)* | 6(55) | 4.6 |
| | *moderate (matig)* | 6(55) | 3.4 |

*Italics* : adjectives not mentioned as such in the original MPQ.

Thirty-eight patients with CIAP (42%) were classified as experiencing neuropathic pain (i.e., as belonging to the NP subgroup or the NP&NNP subgroup) (Table 3). Of the 27 patients in the NP subgroup, 14 (52%) experienced pain in the feet and the lower legs, 10 (37%) experienced pain in the feet, and 3 (11%) experienced pain in the lower legs; 7 patients (26%) also experienced pain in the hands and 2 (7%) experienced pain in the hands and lower arms. All patients in the NNP subgroup experienced nociceptive pain in the head, neck, back, or peripheral joints

of the arms and legs. Fifteen patients (56%) in the NP subgroup were taking medications: anti-epileptic drugs (8 patients), paracetamol (PCM) (6 patients), non-steroid anti-inflammatory drugs (NSAIDs) (3 patients), opioids (3 patients), or tricyclic antidepressants (1 patient). Seven of these patients used a combination of two or three medications, 1 patient used a transcutaneous electrical nerve stimulator, and no information was available for 1 patient. Fifteen patients (60%) in the NNP group were taking medications: NSAIDs (7 patients), PCM (6 patients), and opioids (1 patient). Two patients used two medications and no medication information was available for 1 patient.

Table 3. Demographic characteristics and MPQ-DLV and RAND-36 outcome scores of 63 patients with chronic idiopathic axonal polyneuropathy and pain.

| | | Neuropathic pain n=27 (30%) | Non-neuropathic pain n=25 (27%) | Neuropathic pain and Non-neuropathic pain n=11 (12%) |
|---|---|---|---|---|
| Demographics | Age, years | 65.0 | 68.6 | 66.4 |
| | | (10.3) | (8.1) | (10.0) |
| | Gender (male;female), n | 18;9 | 19;6 | 9;2 |
| | Disease duration, years | 5 | 10 | 9 |
| | | (2-21) | (2-25) | (1-20) |
| MPQ-DLV | Pain duration, years | 4 | 4 | 6 |
| | | (1-20) | (0-35) | (1-19) |
| | Changes in pain over time n(%) | | | |
| | constant severity | 6(22) | 8(32) | 0(0) |
| | varying severity | 17(63) | 12(48) | 11(100) |
| | intermittent | 4(15) | 5(20) | 0(0) |
| | $VAS_{now}$, mm | 33 | 34 | 25 |
| | | (0-69) | (0-64) | (15-70) |
| | $VAS_{min}$, mm | 14 | 16.5 | 17.5 |
| | | (0-69) | (0-61) | (9-38) |
| | $VAS_{max}$, mm | 66 | 64 | 49 |
| | | (21-100) | (26-100) | (28-90) |
| RAND-36 | Physical functioning | 45 | 50 | 35 |
| | | (10-95) | (15-95) | (15-95) |
| | Social functioning | 75 | 87.5 | 75 |
| | | (13-100) | (38-100) | (50-100) |
| | Role limitations physical | 25 | 75 | 50 |
| | | (0-100) | (0-100) | (0-100) |
| | Role limitations emotional | 100 | 100 | 100 |
| | | (0-100) | (0-100) | (0-100) |
| | Mental health | 72 | 80 | 76 |
| | | (28-100) | (32-96) | (52-96) |
| | Vitality | 55 | 60 | 60 |
| | | (15-95) | (35-95) | (30-85) |
| | Pain | 57 | 57 | 57 |
| | | (0-90) | (10-90) | (45-69) |
| | General health perception | 50 | 55 | 40 |
| | | (0-90) | (35-80) | (25-60) |

Values are mean (SD) or median (range) unless stated otherwise.

### Health-related quality of life

The median scores and ranges of the various domains of the RAND-36 varied widely across the patients with and without pain (Table 1), and across the pain subgroups (Table 3). The median score for all pain subgroups for the domain *role limitations due to emotional problems* was 100, indicating that patients with CIAP were not severely affected by such limitations in daily life. The lowest median score was found for the domain *role limitations due to physical problems* among the patients in the NP subgroup (score 25).

### Analysis of correlations between current pain intensity and HRQoL

Low ($r \leq 0.40$)[25], but significant Spearman rank correlation coefficients were found between the $VAS_{now}$ scores and the RAND-36 domain scores in the total patient group (Table 4). Low and non-significant coefficients were found between the $VAS_{now}$ scores and the RAND-36 domain scores in the patient group with pain. Only *physical functioning* was highly and significantly associated with pain among patients in the NP&NNP subgroup (r=-0.71).

Table 4. Spearman correlation of $VAS_{now}$ scores and RAND-36 outcome scores.

| | Study group n=91 (100%) | Pain n=63 (69%) | Neuropathic pain n=27 (30%) | Non-neuropathic pain n=25 (27%) | Neuropathic pain and Non-neuropathic pain n=11 (12%) |
|---|---|---|---|---|---|
| Physical functioning | *-0.27* | **-0.36** | -0.09 | *-0.50* | *-0.71* |
| Social functioning | *-0.22* | -0.08 | 0.16 | -0.38 | -0.03 |
| Role limitations physical | *-0.26* | -0.23 | -0.03 | **-0.53** | -0.09 |
| Role limitations emotional | *-0.23* | -0.21 | -0.18 | -0.31 | 0.00 |
| Mental health | **-0.30** | -0.15 | -0.16 | -0.06 | -0.42 |
| Vitality | **-0.30** | -0.22 | -0.18 | -0.19 | -0.39 |
| General health perception | **-0.33** | -0.22 | -0.04 | -0.38 | -0.44 |

*Italics* : p<0.05; **bold**: p<0.01.

## DISCUSSION

We investigated the prevalence and type of pain experienced by patients with CIAP and whether pain is associated with HRQoL. In total, 69% of the patients reported experiencing pain, with 30% reporting symmetric distal pain (i.e., presumably neuropathic pain), 27% non-neuropathic pain, and 12% a combination of neuropathic and non-neuropathic pain. Pain was 'moderate'[23], with a median VAS score of 33 mm (range 0–70). The pain intensity scores associated with the adjectives most frequently used by patients to describe their pain did not exceed 5.5 points. For most domains of the RAND-36, the HRQoL of the patients with pain was not significantly associated with their pain scores.

We used the MPQ-DLV to investigate whether patients with CIAP experienced pain and used the scale to chart the presence of possible neuropathic pain[26]. The prevalence and nature of purely neuropathic pain in patients with CIAP can be assessed more specifically with the help of new tools[9-11], as has been shown for other patient groups[27]. However, valid Dutch versions of these tests were not available at the time of the study. Since we based the pain classification on the results of the MPQ-DLV and did not take neurological findings into consideration, our classification can only meet the criteria for possible neuropathic pain. The presence of small-fiber neuropathy might have influenced the pain experienced by our patients, but we do not know how many patients with CIAP had small-fiber involvement.

The adjectives most frequently used to describe pain (such as *nagging* and *annoying*) and the corresponding pain intensity scores suggest that the patients experienced 'moderate' pain, which is consistent with the VAS findings. Pain severity may have been influenced by the use of analgesics and by patients' HRQoL[28]. We did not ask patients to stop taking their medication, and thus we evaluated the pain patients experience in everyday life. Anti-epileptic drugs were most frequently used by patients in the NP subgroup and NSAIDs by patients in the NNP subgroup. The five adjectives used most frequently by the NP subgroup did not correspond to those mentioned in other studies using the MPQ[5,6]. Boureau *et al*[6]. found *burning* (54%), *electric shock* (53%), *tingling* (48%), *pricking* (37%), *itching* (33%), and *cold* (22%) to be more frequently used by a heterogeneous group of 100 patients with neuropathic pain compared to patients with non-neuropathic pain. Masson *et al*[5]. found *shooting* (58%), *sharp* (56%), *nagging* (47%), *tingling* (47%), *tiring* (47%), *aching*, *annoying*, *burning*, *cold*, *cramping* (all 44%), *pricking* (39%), and *throbbing* (33%) to be the main pain adjectives chosen by patients with painful diabetic neuropathy. The frequently reported adjectives *electric shock*[6] (53%), *shooting*[5] (58%), and *electric shock-like pain*[29] (59%) were reported by only 24% of our 38 patients from the NP subgroup and the NP&NNP subgroup. The differences in adjective use between our study and those of others may be due to differences in VAS pain scores between the study groups[6], the heterogeneity of the patient populations[6], or the requirement of many studies that patients experience a minimum level of pain as inclusion criterion[28,29].

Although Hughes *et al*.[3] suggested that the HRQoL of their patients with CIAP was worse than that of a reference population, we did not find a clear association between pain and HRQoL. This could be because our patients did not experience severe pain, and the pain they did experience had little influence on HRQoL. It is also possible that the patients with more severe pain had learned to

accept their pain or that analgesic use influenced patients' HRQoL[28]. The lack of a correlation between pain intensity and HRQoL might also be because many patients reported experiencing variable or intermittent pain, but the correlations were calculated for 'pain now'. The median score of 100 in all subgroups for the subscale *role limitations due to emotional problems* might be due to a ceiling effect. Therefore, these results should be interpreted with some caution.

We conclude that patients with CIAP frequently experience pain of variable severity and that neuropathic pain is as common as non-neuropathic pain. We did not find pain to be associated with HRQoL, although findings might have been influenced by patients' use of analgesics. Future studies of CIAP should use new instruments to investigate the prevalence and nature of neuropathic pain syndromes and determine the effects of tailored medical treatment for neuropathic and non-neuropathic pain. As suggested by Dworkin[7], this information could then be used to identify the optimal multidisciplinary approach, including medical treatment, rehabilitation therapy, and psychological interventions.

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# 7

# DISCUSSION

To date, the only functional health profile of patients with polyneuropathy, described in terms of the International Classification of Functioning, Disability and Health (ICF) (WHO, 2001)[1], is that for patients with Guillain-Barré Syndrome (GBS)[2,3]. However, clinical experience shows that the functioning of patients with different polyneuropathies may be different. Clinically relevant effects of treatment and disease progression are difficult to assess with currently available instruments and outcome measures, which often fail to provide detailed insight into aspects that are relevant to patients. Moreover, most currently used instruments are self-report and have broad-grading scales. Little attention has been paid to the development of performance-based tests, yet knowledge of patients' functioning and relevant performance-based tests is needed in order to tailor interventions (e.g., physical training and pharmacology), to determine treatment effects, and to measure disease progression, all of which are important to ensure that patients with polyneuropathy can function optimally. The aim of this thesis was to study the functioning of patients with inflammatory and idiopathic polyneuropathy and determinants of their functioning.

**MAIN FINDINGS**

Investigation of the functional health profiles of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) clearly showed differences between these two patient groups. Patients with CIDP frequently experience problems in walking long distances, whereas patients with MMN frequently experience problems related to their dexterity. These findings emphasized the need to develop specific, relevant performance-based instruments for balance, dexterity, and walking ability, in order to be able to assess patients' functioning in detail. The Sequential Occupational Dexterity Assessment (SODA) and the Shuttle Walk Test (SWT) proved to be interesting tools in this respect. The validity of the SWT was established in patients with CIAP and MMN. The test was found to assess walking ability in a manner that was relevant to patients, and patients reported that the symptoms they experienced at the end of the test were similar to those experienced in daily life. The SWT may thus provide insight into patients' functioning, making it possible to tailor treatment and measure disease progression. The functional health profiles of patients with CIAP and MMN, measured using the SODA and SWT, were different; however, the two tests were highly correlated with patients' functioning, as were muscle strength, fatigue, and age. Lastly, it was found that patients with CIAP often experience pain of both

neuropathic and non-neuropathic origin; however, pain did not significantly influence the health-related quality of life of these patients.

## CONSIDERATIONS

### Functioning

Functional health profiles were created and determinants and instruments were selected based on the problems patients experienced in daily life and on clinical experience. However, longitudinal studies are needed to confirm and extend these profiles. Obviously, the functional health profiles of patients with CIDP, MMN, and CIAP developed in our studies do not fully reflect the dynamic spectrum of patients' functioning, and alternative determinants (e.g., personal and environmental) and additional instruments may provide a broader picture of patients' functioning.

Patients with CIDP and MMN may show different functional health states at different times, e.g., during regular treatment with intravenous immunoglobulin (IVIg). In our studies, patients' functioning was assessed just before they received IVIg in the clinic (chapter 2) and at different times during their course of treatment (chapter 4). Because we do not know) whether the health profiles and associations within the ICF domains would have been different if they had been assessed at different times, it is important, to monitor patients frequently, in both inpatient and outpatient settings, in order to learn about the dynamics of functional health[4]. The formation of databases and the sharing of data with other institutes and centres should be considered, because of the relatively low prevalence of these disorders. This will provide the opportunity to detect additional relevant determinants and changes in patients' functional health status and to evaluate treatment strategies.

The same determinants and instruments were used in the two studies of the functioning of patients with CIAP and MMN, which made comparison between profiles possible. Variance analysis revealed that there were major differences between the two groups of patients. There are a number of potential explanations for these apparent differences. First, other determinants than those measured might be relevant to patients' functioning. Second, it may have been caused by the regression model in which a rejection of an outcome measure (predictor) not only happens when a variable has no relevance to the outcome, but also when other incorporated determinants in the model already supply most of the information the rejected predictor contains[2]. Third, because the associations obtained in the studies were directly linked to the scales used, they might have been different if other instruments were used[2].

**Self-rated and performance-based tests**

The instruments approved by the INCAT group (for patients with inflammatory polyneuropathy)[5], and recommended by the 'European Neuromuscular Centre' (for patients with inflammatory polyneuropathy, diabetic neuropathy, and Charcot-Marie-Tooth neuropathy)[5] contain a broad but relevant spectrum of self-rated tests and rating-scales. In the activity domain, with self-report measures, the individual reports on his or her perceived ability to complete a task or tasks. Besides this highly relevant information, performance-based measures examine the person's ability to complete a task by observing and rating his or her performance[7]. It is recognized that patients are the best source of information, and questionnaires are easy to administer and provide objective representations of subjective feelings[8,9] (e.g., pain, physical functioning and quality of life). However, self-report measures may be biased by aspects, such as depression[10], differences in perceived behaviour control[11], and response shift[12], whereas performance-based measures may be biased by inter-observer bias and lack of coverage of all aspects of interest[13]. The two types of tests are related but distinct[10], and investigators should be aware that the two approaches might test entirely different concepts, experiences, and performance. For instance, in patients with chronic pain, discrepancies have been detected in self-report physical activity and actual level of physical activity[10]. Such a discrepancy was also found in the study reported in chapter 6, where the outcome on the 10MWT and the SWT correlated only moderately with patients' perception of their walking ability assessed with the SF-36. Therefore, both types of instruments should be incorporated in core sets for patients with CIAP and MMN. The use of performance-based tests is essential to enable detailed assessment of problematic activities. Unfortunately, until now the development of performance-based tests in polyneuropathy has received little attention. Because patients with polyneuropathies experience specific activity limitations (dexterity and walking ability), the use of specific performance-based tests (SODA and SWT, respectively) in my opinion is justified.

**CLINICAL IMPLICATIONS AND FUTURE RESEARCH**

Our studies showed that functional health profiles are different in different patient groups, and that functioning needs to be assessed with a core set of relevant instruments suitable for use in a multidisciplinary approach. These profiles and instruments can be used to tailor interventions (e.g., pharmacological therapy and physical training) and monitor the effect of treatment. Core sets for CIAP and MMN

might be complementary to other core sets for polyneuropathies[5,6]. Research should focus on other possible relevant determinants of functioning.

Our findings highlight the need for instruments to assess pain in patients with CIAP. The prevalence and nature of pure neuropathic pain in patients with CIAP can be assessed more specifically with the help of new tools[14-16]. Also, tests are needed to investigate patients' balance in detail, because of its relevance to walking ability, overall functioning, and autonomy in patients with CIDP and CIAP. I recommend the validated SWT as a standard tool to assess the walking ability of patients with CIAP and MMN, especially if the patient cannot walk long distances (e.g., hiking or shopping) but has a normal walking speed over short distances. The SWT is a promising test for the assessment of walking ability because of its established face and concurrent validity. However, its reliability and responsiveness need to be determined, and normative data have to be obtained to enable comparison of the walking ability of patients with polyneuropathy and healthy peers. Clinical experience shows that the SWT also seems to be useful for patients with other types of polyneuropathy. The SWT is currently being used in a cross-sectional study involving patients with polyneuropathy associated with monoclonal gammopathy of undetermined significance. The SODA proved to have internal validity in our studies. Although we did not validate this test as we did with the SWT, the correlation with the Nine Hole Peg test was good (r=-0.81). Extensive investigation of the clinimetric properties of the SODA and factor analysis may create a useful test for evaluating the hand function of patients with MMN in the future.

All the studies had a cross-sectional design, which provided insight into functioning and clinically relevant determinants of functioning. However, the dynamics of functional health and the causes of patient dysfunction need to be investigated in longitudinal studies. These aspects are currently being investigated in a longitudinal study involving patients with CIAP. Preliminary results from this study have already proven useful to patients, by providing information about training and walking aids. The knowledge obtained from this trial and randomized clinical trials will lead to the development of tailored medical and rehabilitation therapies aimed at improving the functional health of patients with polyneuropathy.

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# SUMMARY

The polyneuropathies are a diverse group of diseases affecting peripheral nerves, mostly in the arm(s) and/or leg(s). The disease is usually characterized by symmetrically distributed distal sensory loss ('glove' and/or 'sock' like) and/or muscle weakness of the limbs (hands and/or lower legs/feet). Until the 1990s, the focus of health care for patients with polyneuropathy was mainly on the disease and its accompanying body dysfunctions. Relatively little was known about patients' health in terms of their personal and social functioning. However, since then there has been a growing interest in patients' functional health profiles and patients' health-related quality of life. It seemed appropriate to evaluate the consequences of the disease at a personal and societal level more specifically with help of the International Classification of Functioning, Disability and Health (ICF) framework of the World Health Organization. [Note: The ICF comprises a set of classifications to describe patients' functioning and health. It is structured into three domains: *body functions and structures* (e.g., pain and muscle strength), *activities* (e.g., walking), and social *participation* (e.g., work), together called *functioning*. The ICF also lists *environmental* and *personal factors*. The three domains and environmental and personal factors are supposed to interact mutually with each other]. Studies of functional health profiles are useful because they may provide information about the dynamics of functioning and about which interventions may be beneficial to patients. Moreover, the information obtained may help professionals to select clinimetric instruments appropriate to each type of neuropathy. Efforts to develop instruments to describe and evaluate the functioning of patients with polyneuropathy, and selected inflammatory polyneuropathies (mainly Guillain-Barré syndrome [GBS]), led to the establishment of a world-wide accepted core set of mostly self-rated instruments and scales, based of the ICF framework. Less attention has been paid to the functional health profiles, and determinants thereof, of patients with other polyneuropathies.

The aim of the studies presented in this thesis was to study the functioning of patients with chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), and chronic idiopathic axonal polyneuropathy (CIAP), and to identify determinants of their functioning. Specific research questions were:

1. What are the functional health profiles of patients with different inflammatory polyneuropathies (CIDP and MMN) and do these profiles reveal relevant determinants that can be studied further?
2. How can these determinants be assessed, i.e., what type of clinimetric instruments could be of value in these populations?

3. What are the functional health profiles of patients with CIAP and MMN established with these instruments?
4. What other determinant(s) might influence the functioning of patients with CIAP?

**RESULTS OF THE STUDIES**

In **chapter 2** the functional health profiles of 12 patients with CIDP and 18 patients with MMN were examined in a cross-sectional study using the ICF framework and based on the problems patients experienced in daily life. These profiles were used to identify relevant determinants of functioning and appropriate performance-based instruments to assess functioning. Functional health was assessed using a body function test (hand-held dynamometry [HHD], for maximal isometric muscle strength), three activity tests (10 Meter Walk Test [10MWT], walking ability; Berg Balance Scale [BBS], functional balance; Canadian Occupational Performance Measure [COPM]), and a functioning test (Sickness Impact Profile 68 [SIP68]). Differences in profiles between the two patient groups were apparent. Patients with CIDP most frequently experienced difficulty walking long distances, whereas patients with MMN experienced dexterity problems. These differences were supported by the SIP68 results. However, ceiling effects were detectable in the 10MWT scores and the BBS scores in the patients with MMN, and the scores of both tests varied widely in the patients with CIDP. A clear relationship between the outcomes on most of the instruments was not found. It could therefore be argued that the tests measured different aspects of health. Therefore, for the assessment of patients with inflammatory neuropathy, it is recommended that all ICF domains are investigated, and that appropriate clinimetric instruments specific for each type of neuropathy are used. An appropriate performance-based test for the assessment of dexterity should be used for patients with MMN. An extended performance-based walking test should be used for both groups of patients. The BBS would appear inadequate to assess balance in patients with MMN because of its manifest ceiling effects.

Because there are no specific instruments to assess dexterity and walking ability in patients with polyneuropathy, the Sequential Occupational Dexterity Assessment (SODA) and the Shuttle Walk Test (SWT) were evaluated as instruments to assess these aspects. The SWT was originally developed to assess functional capacity and was validated for the assessment of walking ability in the study reported in **chapter 3**. In this cross-sectional study, 41 patients with CIAP and 49 patients with

MMN were asked whether they considered the 10 Meter Walk Test (10MWT) and the SWT to reflect walking in daily life (Likert scale; 1= not at all, 10=very well), and whether the symptoms they experienced after the SWT were similar to those experienced in daily life (i.e., face validity). The 10MWT, the SWT, the Fatigue Severity Scale (FSS), and the RAND-36 domain physical functioning (RAND-36-PF) were administered to assess the concurrent validity of the SWT. The mean (SD) score for how well the 10MWT and SWT reflected daily walking ability was 6.8 (1.3) and 7.4 (1.6) (n.s.), respectively, in patients with CIAP. These scores were 6.9 (1.2) and 7.9 (1.0) (p=0.001), respectively, in patients with MMN. Spearman rank correlations between the 10MWT and the SWT ranged between -0.70 and -0.82 for most patients in the two groups; patients with MMN who walked at 'normal' speed (based on normative data) during the 10 MWT had a score of -0.21. The correlation between the SWT and the RAND-36-PF ranged from 0.40 to 0.65 in both patient groups. The correlation between the two walking tests and the FSS was ≤ 0.27. It was thus concluded that the SWT is a valid instrument to assess walking ability and related complaints in patients with CIAP and MMN. That is, the test is complementary to the 10MWT and assesses walking ability in a manner that is meaningful and relevant to patients, and the symptoms patients experienced after the SWT were quite similar as to those experienced in daily life.

These results were extended in the cross-sectional study reported in **chapter 4**, in which the functional health profiles and determinants of 56 patients with CIAP were studied in detail. Maximal isometric muscle strength (HHD), sensory modality (sensory modality sum score [SMS]), fatigue (FSS questionnaire), functional balance (BBS), and autonomy (Impact on Participation and Autonomy questionnaire [IPA]) were assessed. The performance-based SODA and SWT were used to investigate dexterity and walking ability, and their feasibility was determined. Muscle strength, fatigue, and walking ability correlated with patients' functioning. That is, muscle strength scores and fatigue scores (and age) explained much of the variance in the walking test scores (63%), and walking test scores in turn explained much of the variance in the autonomy scores (42% and 49%). The SODA and the SWT proved to be feasible performance-based instruments and provided useful detailed information about patients' dexterity and walking ability.

In cross-sectional study described in **chapter 5,** we studied the functional health profiles of 47 patients with MMN, using the same instruments that were used in the study reported in chapter 4 (with exception of the SMS and BBS because of the absence of sensory impairment in MMN and because of ceiling effects of the BBS

in MMN, see chapter 2). Muscle strength, fatigue, and age were found to be related determinants of patients' functioning. Again, muscle strength scores, fatigue scores, and age explained much of the variance in the dexterity and walking ability scores. Strikingly, although many patients experienced limitations in their dexterity and walking ability, the scores on the SODA and SWT did not add much to the variance in the autonomy scores. The functional health profiles of patients with MMN and CIAP (chapter 4) showed differences between these two patient groups. The differences between the SODA scores and SWT scores in both patient groups were clear-cut, showing that patients with MMN suffered more from dexterity problems, whereas patients with CIAP suffered more from walking problems. Walking ability was assessed in both patient groups, with the CIAP patients having the worst scores on the SWT. The SODA and the SWT proved useful for investigating determinants of functioning in patients with MMN, knowledge that will help clinicians to tailor interventions.

Clinical experience has shown that pain is a relevant determinant of the functioning of patients with CIAP. However, the pain these patients experience has never been studied in detail. In the cross-sectional study described in **chapter 6,** the pain experienced by patients with CIAP was investigated using the McGill Pain Questionnaire, and the possible association between pain and health-related quality of life (HRQoL), as assessed with the RAND-36 questionnaire, was investigated. Sixty-three of 91 patients with CIAP reported experiencing pain, describing it as nagging (56%) and annoying (52%). Three blind raters characterized the pain experienced as neuropathic pain (median VAS = 33 mm) in 27 patients, non-neuropathic pain (median VAS = 34 mm) in 25 patients, and mixed pain (median VAS = 25 mm) in 11 patients. Non-neuropathic pain was as common and as painful as neuropathic pain. Pain was strongly associated with the physical functioning domain of the RAND-36 in patients in the mixed pain subgroup ($r=-0.71$, $p< 0.05$). It was concluded that neuropathic and non-neuropathic pain syndromes should be distinguished using specific pain instruments in patients with CIAP, to enable tailoring of treatment.

In summary, functional health profiles were established for patients with CIDP, MMN, and CIAP, and relevant determinants and performance-based instruments were selected. Functional health profiles differed between the patient groups, prominently with regard to dexterity and walking ability. These findings indicated that it is essential to use performance-based tests in order to be able to assess problematic activities in detail. Effective methods to assess the pain experienced

by patients with CIAP, and to assess balance in patients with CIDP and CIAP, are needed. The validated SWT proved to be of value in all patient groups, providing broad insight into patients' walking ability, and is a welcome new test for clinical use. However, the clinimetric properties of the SODA and SWT still have to be determined, as well as normative data.

Future studies with a longitudinal design should examine the dynamics of functional health and the causes of patient dysfunction. Functional health should be monitored frequently, both in inpatient and outpatient settings, to gain an understanding of how functional health status changes with time. The formation of databases and sharing of data both nationally and internationally should be considered, because of the relatively low prevalence of these disorders. Only then will it be possible to detect additional meaningful determinants of, and dynamic changes in, patients' functional health and to develop effective treatment strategies. This knowledge, and that obtained from randomized clinical trials, will lead to the development of tailored medical and rehabilitation therapy aimed at improving the functional health of patients with polyneuropathy.

# SAMENVATTING

Polyneuropathieën zijn aandoeningen waarbij de zenuwen van de armen en benen aangetast worden. Ze worden gewoonlijk gekarakteriseerd door gevoelsstoornissen en/of spierzwakte in de armen en de benen, meestal de handen en/of de onderbenen en de voeten. Tot de jaren negentig was de focus binnen de gezondheidszorg bij patiënten met een polyneuropathie voornamelijk gericht op de ziekte en de erbij behorende gestoorde lichaamsfuncties. Er was nog maar weinig bekend over de gezondheid van de patiënt in termen van zijn persoonlijk en sociaal functioneren. Sinds die tijd is er echter een groeiende interesse ontstaan in de functionele gezondheidsprofielen en de gezondheidsgerelateerde kwaliteit van leven bij deze patiënten. Het leek goed om de consequenties van de aandoening op het persoonlijke en sociale vlak specifiek te gaan onderzoeken met behulp van de 'International Classification of Functioning, Disability and Health' (ICF) van de 'World Health Organization'. [*Noot: De ICF is een raamwerk van classificaties die samen een gestandaardiseerd begrippenapparaat vormen voor het beschrijven van het menselijk functioneren en de problemen die daarin kunnen optreden. Het is opgebouwd uit de drie domeinen lichaamsfuncties en lichaamsstructuren (bijvoorbeeld pijn en spierkracht), activiteiten (bijvoorbeeld lopen) en sociale participatie (bijvoorbeeld werk). Samen worden deze drie het functioneren genoemd. De ICF onderscheid ook nog omgevingsfactoren en persoonlijke factoren. De genoemde domeinen en de factoren worden verondersteld elkaar te beïnvloeden*]. Studies die betrekking hebben op functionele gezondheidsprofielen leveren informatie op over de dynamiek van het functioneren in het dagelijks leven en welke therapieën effectief kunnen zijn voor patiënten. Bovendien kan deze informatie door specialisten gebruikt worden om meetinstrumenten te selecteren welke geschikt zijn voor de verschillende polyneuropathieën. Pogingen om op basis van de ICF meetinstrumenten te ontwikkelen voor het beschrijven en evalueren van het functioneren van patiënten met een polyneuropathie zijn voornamelijk al gedaan voor de acute ontstekingsachtige polyneuropathie, het zgn. Guillain-Barré syndroom. Dit leidde uiteindelijk tot het vaststellen van een wereldwijd geaccepteerde set van meetinstrumenten van meestal vragenlijsten en beoordelingsschalen. Er was tot dan toe minder aandacht voor functionele gezondheidsprofielen, de binnen de gezondheidsprofielen bepalende aspecten (of: 'determinanten') en meetinstrumentontwikkeling bij andere soorten polyneuropathieën.

Het doel van de studies in dit proefschrift was om het functioneren van patiënten met chronische inflammatoire demyeliniserende polyneuropathie (CIDP),

multifocale motorische neuropathie (MMN) en chronische idiopathische axonale polyneuropathie (CIAP) te bestuderen en om determinanten binnen het functioneren te identificeren. De specifieke onderzoeksvragen waren:

1. Wat zijn de functionele gezondheidsprofielen van patiënten met verschillende ontstekingsachtige polyneuropathieën (CIDP en MMN) en leveren deze profielen relevante determinanten op voor verdere studie?
2. Hoe kunnen deze determinanten worden onderzocht, oftewel, welke meetinstrumenten zouden van waarde kunnen zijn voor gebruik in deze patiënten populaties?
3. Hoe zien de functionele gezondheidsprofielen eruit van patiënten met CIAP en MMN wanneer gebruik gemaakt wordt van deze meetinstrumenten?
4. Welke andere determinant(en) zou(den) het functioneren van patiënten met CIAP mogelijk kunnen beïnvloeden?

**RESULTATEN VAN DE STUDIES**

In **hoofdstuk 2** werden de functionele gezondheidsprofielen van 12 patiënten met CIDP en 18 patiënten met MMN onderzocht in een cross-sectionele studie met behulp van de ICF en op basis van de ervaren problemen van de patiënten uit het dagelijks leven. Deze profielen werden gebruikt om relevante determinanten binnen het functioneren en geschikte 'performance-based' meetinstrumenten te ontdekken. De functionele gezondheidstoestand werd gemeten met een functietest (hand-held dynamometrie [HHD], voor de bepaling van de maximale isometrische spierkracht), drie activiteiten tests (10 Meter Looptest [10MWT], loopvaardigheid; de Berg Balance Scale [BBS], functionele balans; Canadian Occupational Performance Measure [COPM]) en een functionele test (Sickness Impact Profile 68 [SIP68]). Er bleken verschillen tussen de profielen van de twee groepen patiënten te bestaan. Patiënten met CIDP ervoeren het meest frequent problemen met het lopen van lange afstanden, terwijl de patiënten met MMN het meest problemen met de handvaardigheid ervoeren. Deze verschillen werden bevestigd door de resultaten vanuit de SIP68. Er waren plafondeffecten aanwezig in de scores van de 10MWT en de BBS bij de patiënten met MMN, terwijl de scores van deze beide testen erg verschillend waren bij de patiënten met CIDP. Er werden geen duidelijke relaties tussen de scores van de meeste meetinstrumenten gevonden. Daarom kan er gesteld worden dat de verschillende testen verschillende aspecten van gezondheid meten. Daarom wordt aanbevolen om bij patiënten met een ontstekingsachtige polyneuropathie op alle domeinen binnen de ICF onderzoek te doen en wordt aanbevolen geschikte meetinstrumenten te gaan gebruiken bij elk

type polyneuropathie. Voor de handvaardigheid zou een geschikte 'performance-based' test gebruikt moeten worden. Evenzo zou een 'performance-based' test voor de loopvaardigheid gebruikt moeten gaan worden voor beide patiëntengroepen. De BBS bleek niet adequaat om de balans te meten bij patiënten met MMN vanwege de duidelijke plafondeffecten in de scores.

In het vervolg van de studies werden de Sequential Occupational Dexterity Assessment (SODA) en de Shuttle Walk Test (SWT) gebruikt om de handvaardigheid en de loopvaardigheid te meten bij patiënten met een polyneuropathie, omdat er geen specifieke meetinstrumenten zijn om deze aspecten te meten bij deze patiëntengroep. De SWT welke oorspronkelijk ontwikkeld is voor het meten van de functionele (long)capaciteit werd gevalideerd voor de bepaling van de loopvaardigheid in de gerapporteerde studie in **hoofdstuk 3**. In deze cross-sectionele studie werd aan 41 patiënten met CIAP en 49 patiënten met MMN gevraagd, nadat zij de twee testen gelopen hadden, in hoeverre de 10MWT en de SWT hun loopvaardigheid in het dagelijks leven weergaven (Likert schaal; 1=helemaal niet, 10=erg goed) en of de symptomen die zij ervoeren na de SWT gelopen te hebben overeenkwamen met die uit het dagelijks leven ('face' validiteit). De 10MWT, de SWT, de Fatigue Severity Schaal (FSS) en de RAND-36 domein fysiek functioneren (RAND-36-PF) werden afgenomen om de concurrent validiteit van de SWT te bepalen. De gemiddelde (SD) score voor de mate van weergave van de loopvaardigheid door de 10MWT en de SWT was respectievelijk 6.8 (1.3) en 7.4 (1.6) (n.s.) voor de patiënten met CIAP. De scores waren respectievelijk 6.9 (1.2) en 7.9 (1.0) (p=0.001) voor patiënten met MMN. De Spearman rank correlatie tussen de 10MWT en SWT kende een range van -0.70 tot -0.82 voor de meeste patiënten in de twee groepen; patiënten met MMN die (gebaseerd op normatieve data) een normale loopsnelheid hadden op de 10MWT hadden een score van -0.21. De correlatie tussen de SWT en de RAND-36-PF kende een range van 0.40 tot 0.65 in beide patiënten groepen. De correlaties tussen de 10MWT en de SWT enerzijds en de FSS anderzijds waren ≤ 0.27. Er werd geconcludeerd dat de SWT een valide meetinstrument is om de loopvaardigheid en de hieraan gerelateerde klachten te meten bij patiënten met CIAP en MMN. Dat wil zeggen, de test is complementair aan de 10MWT en de test meet de loopvaardigheid op een manier die betekenisvol en relevant is voor de patiënt. Tevens waren de symptomen welke de patiënten ervoeren na de SWT gelopen te hebben gelijk aan die zij ervoeren in het dagelijks leven.

De resultaten uit de beschreven studie in hoofdstuk 3 werden gebruikt in de cross-sectionele studie in **hoofdstuk 4**. In deze studie werden de functionele gezondheidsprofielen en -determinanten van 56 patiënten met CIAP in detail bestudeerd. De maximale isometrische kracht (HHD), de sensoriek (sensory modality sum score [SMS]), de vermoeidheid (FSS), de functionele balans (BBS) en autonomie (Impact on Participation and Autonomy questionnaire [IPA]) werden gemeten. De 'performance-based' testen SODA en SWT werden gebruikt om de handvaardigheid en de loopvaardigheid te onderzoeken, evenals de toepasbaarheid van deze testen. De spierkracht, de vermoeidheid en de loopvaardigheid bleken te correleren binnen het functioneren van de patiënten. Dat wil zeggen, de spierkracht- en vermoeidheidscores (en leeftijd) verklaarden veel van de variantie van de loopvaardigheid-scores (63%) en de loopvaardigheid-scores verklaarden vervolgens veel van de variantie van de autonomie-scores van de patiënten (42% and 49%). De SODA en de SWT bleken goed toepasbare meetinstrumenten en zij gaven nuttige gedetailleerde informatie met betrekking tot de handvaardigheid en loopvaardigheid van de patiënten.

In de beschreven cross-sectionele studie in **hoofdstuk 5** bestudeerden we de functionele gezondheidsprofielen van 47 patiënten met MMN met dezelfde meetinstrumenten uit de studie uit hoofdstuk 4 (met uitzondering van de SMS en de BBS vanwege het ontbreken van sensorische stoornissen bij patiënten met MMN en vanwege de plafondeffecten van de BBS bij gebruik bij patiënten met MMN, zie hoofdstuk 2). De determinanten spierkracht, vermoeidheid en leeftijd waren gerelateerd aan het functioneren van de patiënten. Opnieuw verklaarden de scores van de spierkracht, de vermoeidheid en de leeftijd veel van de variantie van de scores op de handvaardigheid en de loopvaardigheid. Opvallend genoeg droegen de scores van de SODA en de SWT niet veel bij aan de variantie van de autonomie scores, hoewel veel patiënten wel beperkingen ervoeren met betrekking tot de handvaardigheid en de loopvaardigheid. De functionele gezondheidsprofielen tussen de patiënten met MMN en de patiënten met CIAP (hoofdstuk 4) waren verschillend. De verschillen tussen de SODA scores en de SWT scores in beide patiëntengroepen waren duidelijk aanwezig; patiënten met MMN kenden meer beperkingen met betrekking tot hun handvaardigheid, terwijl patiënten met CIAP meer beperkingen kenden met betrekking tot hun loopvaardigheid. De loopvaardigheid werd onderzocht in beide patiëntengroepen, waarbij de patiënten met CIAP op de SWT de slechtste scores hadden. De SODA en de SWT bewezen van nut te zijn voor het onderzoeken van determinanten

binnen het functioneren van patiënten met MMN. Met deze kennis kunnen clinici hun interventies beter sturen.

De klinische ervaring leert dat pijn een relevante determinant is binnen het functioneren van patiënten met CIAP. Echter, de pijn die ze ervaren is nog nooit in detail onderzocht. In de cross-sectionele studie welke beschreven is in **hoofdstuk 6** werd de ervaren pijn bij patiënten met CIAP onderzocht met behulp van de McGill Pain Questionnaire. Tevens werden de relaties onderzocht tussen pijn en de gezondheidgerelateerde kwaliteit van leven zoals gemeten met de RAND-36 questionnaire. Drieënzestig van de 91 onderzochte patiënten met CIAP ervoeren pijn welke omschreven werd als zeurend (56%) en hinderlijk (52%). Drie geblindeerde beoordelaars classificeerden de ervaren pijn van de patiënten als neuropathische pijn (mediaan VAS = 33 mm) bij 27 patiënten, niet-neuropathische pijn (mediaan VAS = 34 mm) bij 25 patiënten en gecombineerde vormen van pijn (mediaan VAS = 25 mm) bij 11 patiënten. De niet-neuropathische pijn kwam evenveel voor en werd als even erg ervaren als de neuropathische pijn. De pijn was sterk gerelateerd aan met het domein fysiek functioneren van de RAND-36 bij patiënten uit de gecombineerde pijn groep ($r = -0.71$, $p < 0.05$). Geconcludeerd werd dat neuropathische en niet-neuropathische pijn onderscheiden zou moeten worden met gebruik van specifieke meetinstrumenten bij patiënten met CIAP met als doel om behandeling te richten.

Samenvattend werden er functionele gezondheidsprofielen opgesteld voor patiënten met CIDP, MMN en CIAP en werden er relevante determinanten en 'performance-based' meetinstrumenten geselecteerd. De functionele gezondheidsprofielen tussen de patiëntengroepen waren verschillend, vooral met betrekking tot de handvaardigheid en de loopvaardigheid. De resultaten geven aan dat het essentieel is om 'performance-based' meetinstrumenten te gebruiken om beperkingen in activiteiten in detail te kunnen weergeven. Het is noodzakelijk om effectieve methoden te ontwikkelen om pijn (bij patiënten met CIAP) en balans (bij patiënten met CIDP en CIAP) te kunnen meten. De gevalideerde SWT bleek van waarde bij alle patiëntengroepen doordat hiermee een breed inzicht verkregen werd in de loopvaardigheid. Het is een welkome nieuwe test voor klinisch gebruik. Echter, de klinimetrische eigenschappen en normatieve data van de SODA en de SWT moeten nog bepaald worden.

In toekomstige studies met een longitudinaal design moeten de dynamiek binnen de functionele gezondheid en de oorzaken van het beperkt functioneren van patiënten onderzocht worden. De functionele gezondheid moet meer frequent

onderzocht worden, zowel in de klinische als ook in de poliklinische setting, om de veranderingen in de functionele gezondheidstoestand in de tijd te kunnen zien. Omdat de onderzochte aandoeningen een relatief lage prevalentie kennen moet overwogen worden om databestanden op te zetten (en het uitwisselen hiervan), zowel nationaal als internationaal. Alleen dan is het mogelijk om aanvullende betekenisvolle determinanten van en dynamische veranderingen in de functionele gezondheid van de patiënten te ontdekken en om effectieve behandelingsstrategieën te ontwikkelen. Deze kennis en die vanuit gerandomiseerde klinische onderzoeken zal leiden tot de ontwikkeling van op maat gesneden medische en revalidatie therapie met als doel om de functionele gezondheid bij patiënten met een polyneuropathie te verbeteren.

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# CURRICULUM VITAE

Peter Erdmann werd op 15 april 1964 geboren te Loosdrecht. Hij behaalde het VWO diploma in 1985 aan de Rembrandtschool te Hilversum. Aansluitend begon hij aan de studie fysiotherapie aan de Academie voor Fysiotherapie 'Thim van der Laan' te Utrecht. De studie werd in 1989 afgerond met het diploma. Terwijl diverse waarnemingen fysiotherapie elkaar opvolgden werd in dat jaar begonnen met de studie Bewegingswetenschappen aan de Vrije Universiteit te Amsterdam. Na het propedeusejaar koos hij voor de vakgroep Bewegingsagogiek. Na het behalen van het doctoraalexamen in 1993 kreeg hij aan het einde van hetzelfde jaar een vaste aanstelling als fysiotherapeut binnen het toenmalige Centrum voor Paramedische Behandeling en Revalidatie van het Academisch Ziekenhuis Utrecht. Tot 1997 was hij vanuit dit centrum vooral klinisch werkzaam op de Afdeling Orthopedie. Vanaf medio 1997 tot en met heden is hij, vanuit de nu zo geheten Afdeling Revalidatie, Verplegingswetenschap en Sport van het Universitair Medisch Centrum Utrecht, klinisch werkzaam op de Afdeling Neurologie. De (poli)klinische patiëntenzorg spitste zich vanaf 1997 langzaam meer toe op het gekozen aandachtsgebied neuromusculaire ziekten. Rond 2000 werd een start gemaakt met het wetenschappelijk onderzoek bij patiënten met polyneuropathieën met 0.5 fte onderzoekstijd. Een promotietraject volgde in 2005 met 0.5 fte onderzoekstijd. Tevens is hij sinds 1999 actief betrokken bij de Vereniging Spierziekten Nederland. Sinds 2007 is hij er medisch adviseur binnen de werkgroep Guillain-Barré syndroom, CIDP en MMN.