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.

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 [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 to 108. 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 1 m 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 (n = 32) aged 50 to 70 years of the original SWT range from mean (SD) 699 (122) m to 727 (161) m [21].

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 [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, 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 \( \geq 45 \) 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\(_{\text{indoors}}\) whereas 17 patients scored 2.0 or more on IPA\(_{\text{outdoors}}\), which means that they experienced significant problems in autonomy outdoors. The IPA\(_{\text{indoors}}\) item my chances of getting around in my house where I want to are... (mean 1.11) and the IPA\(_{\text{outdoors}}\) 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.

### Correlation studies

Moderate Pearson correlation coefficients were found between the IPA\(_{\text{indoors}}\) and IPA\(_{\text{outdoors}}\) 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.) respec-

### 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 (8.6)              | 66.1 (8.4)               | 67.7 (8.9)               | 73 (7.1)                |
| Gender (male; female, n)             | 45;11                   | 15;4                     | 25;5                     | 5;2                     |
| Disease duration, years              | 10.5 (6.5)              | 9 (6.4)                  | 11 (6.8)                 | 12.6 (5.6)              |
| Arm functioning                      |                         |                          |                          |                         |
| Maximal isometric strength (HHD, z-score) | −0.1 (0.9)          | 0.4 (0.7)                | −0.2 (0.8)               | −0.7 (1.1)              |
| Sensory function (SMS, 0–28 points) | 28.0 (6 to 28)          | 28 (26 to 28)            | 27.5 (6 to 28)           | 26 (17 to 28)           |
| Pain (n%)                            | 20 (36)                 | 4 (21)                   | 13 (43)                  | 3 (43)                  |
| Dexterity (SODA, 0–108 points)      | 105.0 (76 to 108)       | 106 (97 to 108)          | 102 (82 to 108)          | 96 (76 to 108)          |
| Leg functioning                      |                         |                          |                          |                         |
| Maximal isometric strength (HHD, z-score) | −1.9 (1.0)          | −1.2 (0.7)               | −2.1 (0.9)               | −2.6 (0.9)              |
| Sensory function (SMS, 0–28 points) | 15.0 (4 to 28)          | 16 (9 to 28)             | 15 (5 to 22)             | 13 (4 to 18)            |
| Pain (n%)                            | 43 (77)                 | 15 (79)                  | 24 (80)                  | 4 (57)                  |
| Walking perf. (SWT, 0–150 10-m. courses) | 60.4 (44.6)          | 101.0 (37.9)             | 44.9 (32.3)              | 16.3 (14.8)             |
| Use of walking aids (n%)             | 18 (32)                 | 1 (5)                    | 11 (37)                  | 6 (86)                  |
| Fatigue (FFS, 1–7 points)            | 4.5 (1 to 7)            | 2.7 (1.0 to 5.4)         | 5.2 (1.7 to 7.0)         | 5.3 (1.6 to 7.0)        |
| Balance (BBS, 0–56 points)           | 54.0 (13 to 56)         | 56 (48 to 56)            | 54 (30 to 56)            | 22 (13 to 56)           |
| Autonomy indoors (IPA, 0–4 points)   | 1.0 (0 to 2.1)          | 0 (0 to 1.7)             | 1.0 (0 to 2.1)           | 1.1 (0.6 to 1.9)        |
| Autonomy outdoors (IPA, 0–4 points)  | 1.4 (0 to 3.4)          | 0.6 (0 to 1.6)           | 1.8 (0 to 2.8)           | 2.4 (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
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. Again, the results were not substantially different after adjustment for age and the use of walking aids. All percentages were significant ($p < 0.01$).

### 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/hour. 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. (accepted) [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 cor-

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

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

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; IPA indoors, impact on participation and autonomy questionnaire, sub-scale autonomy indoors; IPA outdoors, impact on participation and autonomy questionnaire, sub-scale autonomy outdoors.
related 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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