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RESEARCH REPORT

Impairment and disability in 20 CIDP patients according to disease activity status

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Abstract Twenty patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) meeting the EFNS/PNS criteria were examined in order to assess differences/similarities between the various grading systems according to CIDP disease activity status (CDAS). A principal component (PC) analysis and the correlations between the following scores were performed: Neurological Symptom Score; MRC sum score; Neurological Impairment Score; Hammersmith Functional Motor Scale; Inflammatory Neuropathy Cause and Treatment (INCAT) Sensory Sum Score; Overall Disability Sum Score; INCAT Disability Score; Rasch-built Overall Disability Scale. Our analysis outlined two main sets of scales, with high influence in the top two PCs. The first PC that best explained the variability within the cohort consisted of CDAS, general disability scores and motor scores; these parameters were also strongly correlated amongst each other. The second PC explained less the variability and consisted mainly of sensory scores and disease duration; these parameters did not correlate with the scores of the first PC or with the CDAS. Our findings suggest separating screening for motor and sensory deficits when evaluating CIDP patients, as only the motor scores correlate with CDAS.

Key words: CDAS, CIDP, grading systems, R-ODS, scores

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune neuropathy with high clinical heterogeneity leading to various degrees of disability. Expert consensus is available for diagnosis and treatment *(Joint Task Force of the EFNS and the PNS, 2010)*. For diagnosis and assessment of treatment effectiveness, a series of grading systems have been proposed by the Inflammatory Neuropathy Cause and Treatment (INCAT) group and others: (1) *general disability scores*, such as Neurological Impairment Score *(Dyck et al., 1980)*, Neurological Symptom Score *(Dyck et al., 1980)*, INCAT Disability Score *(Hughes et al., 2001)*, INCAT Overall Disability Sum Score *(Merkies et al., 2002)* or the Rasch-built Overall Disability Scale *(van Nes et al., 2011)*; (2) *motor scores*, such as Medical Research Council Sum Score *(Dyck et al., 2005)*, Hammersmith Functional Motor Scale *(Scott et al., 1982)* and motor component of NIS; (3) *sensory scores*, such as INCAT Sensory Sum Score *(Merkies et al., 2000)* or the sensory component of NIS. Recently, a grading system assessing disease activity in relation to treatment status, the CIDP disease activity status (CDAS) *(Gorson et al., 2010)*, has been developed to complement the disability and impairment scales and is applicable in both clinical practice and research studies.

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Our goal is to analyze a series of CIDP patients using current clinical scores, to establish a relationship between scores and to examine correlations of the scores with CDAS.

Patients and Methods

Patients

Twenty-five patients fulfilling the EFNS/PNS criteria for CIDP were contacted to participate in this study. Twenty agreed to take part in this study and provided informed consent. This study was approved by the hospital's ethics committee.

Assessed scales

Between May and December 2011, every patient underwent a neurological examination by two investigators. The following grading systems were evaluated:

General scores and scales:

1 Neurological Symptom Score (NSS) *(Dyck et al., 1980; Herndon, 2005)*.
2 Neurological Impairment Score (NIS) *(Dyck et al., 1980)*.
3 Inflammatory Neuropathy Cause and Treatment Group (INCAT) Overall Disability Sum Score (ODSS) *(Merkies et al., 2002)*.
4 INCAT Disability Score (INCAT DS) *(Hughes et al., 2001)*.

Motor scores:

1 Hammersmith Functional Motor Scale (HFMS) *(Scott et al., 1982)*.
2 Medical Research Council Sum Score (MRC) *(Dyck et al., 2005)*.
3 Rasch-built Overall Disability Scale (R-ODS) *(van Nes et al., 2011)*.

Sensory score:

1 The INCAT Sensory Sum Score (ISS) *(Merkies et al., 2000)*.

The CIDP disease activity status (CDAS) (Standard CDAS, see Table 1)

We intended to assess the relationship between CDAS and the clinical grading systems. However, the categories 1 to 4 in CDAS each include a subcategory for patients with normal examination. Therefore, in order to make valid comparisons, we modified the CDAS (Modified CDAS, see Table 1), pooling the subcategories of patients with normal examination as 0; the remaining subcategories are distributed from 1 to 7 in the following order: 1-cured (1B in standard CDAS), 2-in remission (2B), 3-stable active disease (3B), 4-improving (4B), and 5-unstable active disease with naïve treatment (5A), 6-off treatment (5B), or 7-on treatment (5C).

Table 1. Proposed modified numerical version of CDAS.

Standard CDAS	Modified CDAS
1. Cured: ≥5 years off treatment	
A. Normal examination	0
B. Abnormal examination, stable/improving	1
2. Remission: <5 years off treatment	
A. Normal examination	0
B. Abnormal examination, stable/improving	2
3. Stable active disease: ≥1 year on treatment	
A. Normal examination	0
B. Abnormal examination, stable/improving	3
4. Improvement: ≥3 months <1 year on treatment	
A. Normal examination	0
B. Abnormal examination, stable/improving	4
5. Unstable active disease: abnormal examination with progressive or relapsing course	
A. Treatment naïve or <3 months	5
B. Off treatment	6
C. On treatment	7

The different subcategories of CDAS were renumbered on a numerical scale, with 0 for asymptomatic patients and distributing the other subcategories with abnormal examination from 1 to 7.
CDAS, chronic inflammatory demyelinating polyradiculoneuropathy disease activity status.

Statistics

The data obtained for each evaluated scale was checked for normality and transformations were applied when necessary. Using JMP 10.0 statistical software (SAS Institute Inc., Cary, NC, USA) we performed a principal component analysis (PCA) on correlations on the group of evaluated scales and patient characteristics. PCA visualizes the structure of a data set as completely as possible using as few variables as possible. It derives a small number of independent linear combinations (principal components, PCs) of a set of variables, capturing as much of the variability in the original variables as possible. When analyzing a number of original variables, an equal number of PCs uncorrelated with each other is formed, in decreasing order of greatest possible variance *(SAS Institute Inc., 2012)*. The Pearson's correlations for the assessed variable were also calculated by JMP 10.0 statistical software as a by-product of the PCA, and were analyzed for a more in depth view of the PCA results.

Table 2. Clinical characteristics of the studied cohort (n = 20 patients).

Age (years)	
<40	15%
40–65	45%
65+	40%
Male gender	70%
Caucasian	100%
History of spontaneous relapses	25%
Symmetric onset	90%
Sensory symptoms	
None	10%
Asymmetric	5%
Both sides	85%
Facial weakness	0%
Symmetric on motor exam	95%
Distal weakness on exam	
No limbs	55%
1–3 limbs	30%
All four limbs	15%
Proximal weakness on exam	
None	55%
1–3 limbs	25%
All four limbs	15%
Number of absent/hypoactive reflexes	
None	5%
1–9	35%
All 10	60%
Abnormal sensory function	
No	10%
Asymmetric	5%
Symmetric	90%
Evidence of demyelination on biopsy	
Biopsy not done	90%
No	0%
Yes	10%
Evidence of axon loss on biopsy	
No	0%
Yes	10%
CSF protein (mg/dl)	
≤45	15%
>45	65%
Not tested/data not available	20%
CSF cells (number/μl)	
<10	80%
≥10	0%
Not tested/data not available	20%

Results

Cohort clinical characteristics

The group of patients consisted of 14 men and 6 women who had a mean duration of symptoms of 5.9 years. None of the patients had normal examination; one was bed-bound while another required crutches to walk short distances. Fifty percent of the patients had stable active disease, 35% were in remission, 10% were unstable with active disease and 5% were improving. A summary of the clinical features is provided in Table 2 and an overview of the grading system results is in Table 3.

Table 3. Results of the evaluated grading systems.

	Average (range)	Normal value
ISS	3.1 (1–7)	0
NSS	3.5 (1–8)	0
S-NIS	7.8 (1–16)	0
M-NIS	9.6 (0–52)	0
HFMS	34.7 (10–40)	40
MRC	55.7 (44–60)	60
NIS	29.2 (2–80)	0
ODSS	1.9 (0–9)	0
INCAT DS	1.6 (0–8)	0
R-ODS	41.1 (10–48)	48

CDAS, CIDP disease activity status; HFMS, Hammersmith Functional Motor Scale; INCAT, Inflammatory Neuropathy Cause and Treatment; INCAT DS, INCAT Disability Score; ISS, INCAT Sensory Sum Score; MRC, Medical Research Council Sum Score; M-NIS, motor scores of NIS; NSS, Neurological Symptom Score; ODSS, Overall Disability Sum Score; R-ODS, Overall Disability Scale; S-NIS, sensory scores of NIS.

Principal component analysis

Thirteen PCs resulted from the PCA and the PCs 1–5 are shown in Table 4. The first two PCs explained more than 80% of the variability within the group. The motor scores, disability scales and CDAS contributed substantially to the first PC (the linear combination of the standardized original variables that has the greatest possible variance) and explained 55% of the variability, while the disease duration and sensory scores had high influence in the second PC and accounted for 25% of the variability. The graphical representation of the loading plot for these two PCs showed the similarities of the original variables, creating clusters on the axis (Fig. 1). CDAS and NIS had major contributions to the first PC, but also had moderate fractions in the second PC, while disease duration and S-NIS contributed moderately to another PC besides the second PC. Age and NSS did not contribute significantly to the first two PCs; however, they had moderate input in several PCs, revealing other components of the clinical picture besides motor or sensory findings.

Correlation analysis

The correlation analysis demonstrated why the PCA yielded two main subgroups of grading systems (Table S1, Supporting Information), with strong correlations inside the groups of scores and scales (motor or sensory impairment, disability), between the motor and disability scores, but not between the sensory scores and the other groups. Age did not correlate with any score, while the disease duration correlated with both of the sensory scores, but none of the disability or motor impairment scales. As shown by the PCA, the CDAS correlated with the motor impairment scores and strongly with the disability

Table 4. Loading matrix of the first five principal components.

	PC1 (55.7%)	PC2 (25.6%)	PC3 (6.2%)	PC4 (4.3%)	PC5 (3.4%)
CDAS	**0.80**	*−0.39*	0.19	−0.15	0.17
Age	−0.18	*0.63*	*0.57*	*−0.46*	−0.09
Duration	0.17	**0.85**	−0.17	0.12	*−0.37*
ISS	0.06	**0.95**	−0.06	0.07	0.06
S-NIS	0.13	**0.86**	−0.08	0.00	*0.45*
NSS	*0.71*	*0.33*	*0.42*	*0.39*	−0.07
M-NIS	**0.96**	−0.01	−0.15	−0.06	0.00
HFMS	**−0.90**	0.07	0.23	0.20	0.07
MRC	**−0.89**	−0.12	0.21	0.25	0.16
NIS	**0.87**	*0.39*	−0.12	0.00	0.10
ODSS	**0.93**	−0.20	0.19	0.04	−0.07
INCAT DS	**0.92**	−0.21	0.20	0.15	0.01
R-ODS	**−0.97**	0.11	0.02	−0.02	−0.06

The principal component (PC) analysis of the studied scores and scales showed 13 PCs, with eigenvalue percentages ranging from 55.7% to 0.009%. The first five PCs, with eigenvalue percentages of >2%, are presented in the table, with the loading factor for each variable (age and grading systems). Bold values indicate high component loading values for the variable, while italic values indicate a medium contribution to the PC. The components that have major contributions (absolute fractions > 0.8) to the first two PCs clearly form two distinctive subgroups: (1) motor scores, disability scales and CDAS; and (2) sensory scores and disease duration.
CDAS, CIDP disease activity status; HFMS, Hammersmith Functional Motor Scale; INCAT, Inflammatory Neuropathy Cause and Treatment; INCAT DS, INCAT Disability Score; ISS, INCAT Sensory Sum Score; MRC, Medical Research Council Sum Score; M-NIS, motor scores of NIS; NSS, Neurological Symptom Score; ODSS, Overall Disability Sum Score; R-ODS, Overall Disability Scale; S-NIS, sensory scores of NIS.

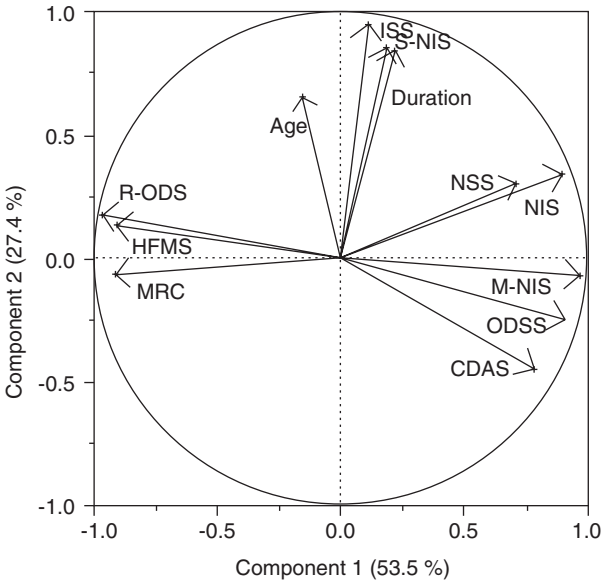

Figure 1. Loading plot of the first two principal components (PCs). The PC analysis revealed that the first two PCs contributed together to more than 80% to the variability of the group of scores and scales. The two-dimensional representations of factor loadings of these two PCs shows clustering along the axis of disability scales (R-ODS, ODSS, INCAT DS) and motor scores (M-NIS, MRC and HFMS) for the first PC; and the disease duration and sensory scores (ISS, S-NIS) for the second PC, describing two distinct characteristics of the disease. These scores and scales either do not correlate, or correlate strongly with the CDAS. The scores evaluating both motor and sensory impairment (NIS and NSS) form a separate cluster, while age does not contribute significantly to the first two PCs.

scales, but not with the sensory scores, age of patients, or disease duration.

Discussion

The large spectrum of clinical manifestations is a hallmark of CIDP. A number of clinical scores and scales have been proposed to assess the clinical course and treatment outcome, evaluating several levels of impairment, disability, or quality of life, and to estimate the short-term effect of treatment *(Dyck et al., 1982; Mendell et al., 2001; Hughes et al., 2008; van Schaik et al., 2010)*. Recently, a disease activity status scale (CDAS) has been developed that focuses on the long-term evolution of CIDP *(Gorson et al., 2010)*.

This study analyzed the relationship between some of the scores used in clinical practice or research in order to establish if any of them correlate to the CDAS. As our cohort did not include cured patients or patients with normal examination *(Gorson et al., 2010)*, and in order to make valid comparisons, we used a modified CDAS where the classes with normal examination were pooled at zero on the scale (Table 1).

The scales with the most important contributions to the first two PCs yielded from our PCA form two clear clusters along the orthogonal axis in the graphical representation (Fig. 1), delineating two distinct subgroups: (1) motor scores, disability scales and CDAS; and (2) sensory scores and disease duration. The two clusters are virtually perpendicular and the component variables do not correlate with each other (Table S1), indicating the possibility that the subgroups describe different characteristics of CIDP. The strong correlation between motor scores and the disability scales confirms the assertion that disability is mainly due to the motor impairment *(Merkies et al., 2002; van Nes et al., 2011)*, although this association was expected as the scales used are designed to measure primarily the motor deficit.

Age, disease duration, NSS, and NIS supply notable fractions (>0.25) to more than one PC, indicating multiple contributions to the variability of the group and to the phenotype of patients in the studied cohort (Table 4). NSS and NIS form a third intermediate cluster on the first diagonal, given that they evaluate more than one type of deficit (Fig. 1). Age does not appear to play a role in the disease manifestations in the studied cohort. It does not cluster with any scale in the first two PCs, nor correlates

with any of the motor or general disability grading systems, and there is only a very slight correlation with the sensory scores, as reported in other studies *(Merkies et al., 1999)* indicating that age does not play a role in the severity of the disease. In contrast, there is a clear association between disease duration and sensory scores ($R = 0.63$ vs. S-NIS and $R = 0.8$ vs. ISS), which is in accordance with our clinical experience, that even in aggressively treated CIDP patients, the sensory deficits often persist distally, with or without neuropathic pain, and may reflect irreversible axonal loss, but rarely contribute to functional disability.

Comparing the modified CDAS with the evaluated clinical characteristics and scales, we found that it correlates strongly with the disability scales and to a slightly lesser extent with the motor scores, and that it presents either no or very little association with age, disease duration or the scores that also evaluate sensory symptoms. This finding supports the existence of a link between CDAS, disability and motor deficit in the studied cohort, while the sensory impairment has only a minor influence on the CDAS. Given that CDAS evaluates the disease activity based on the presence or the follow-up of a treatment, we can infer that the sensory scales might have a limited utility when assessing the outcome in CIDP patients during follow-up and in clinical trials.

Limitations to this study include the size of the cohort. We also had to normalize some of the nonlinear variables in order to analyze our data. For clarity, we presented only the results obtained from the PCA; however, a complementary analysis using Spearman's test for nonparametric data had yielded similar correlation results. Further, data from nerve conduction studies were not incorporated in the correlation analysis due to the variability in the parameters.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Correlation coefficients between the analyzed scores and scales.