Quantitative grip force assessment of muscular weakness in chronic inflammatory demyelinating polyneuropathy

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Abstract

Background: In patients suffering from Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) disease severity is assessed by Medical Research Council (MRC) Scale or Inflammatory Neuropathy Cause and Treatment (INCAT) disability score. However, none of these methods is appropriate to objectively assess muscle weakness or to detect very small subclinical changes. More objective and quantitative measures are needed in order to evaluate treatment efficiency or to detect subclinical affection of upper limps for early diagnosis. The goal of our study was to objectively quantify muscular weakness in CIDP patients with the non-invasive Quantitative Motor (Q-Motor) test of Grip Force Assessment (QGFA) as well as the Involuntary Movement Assessment (QIMA) and to search for differences between typical and atypical CIDP variants. In addition, we hypothesized that Q-Motor findings correlate with disease severity scales such as MRC or INCAT score.

Methods: In this cross-sectional exploratory proof-of-concept study subjects with confirmed diagnosis of typical or atypical CIDP were examined and compared to healthy controls (HC). For Q-Motor tests all subjects had to lift a device (250 g and 500 g) equipped with an electromagnetic sensor that measured grip force (GF) and three-dimensional changes in position and orientation. The measures “grip force variability” (GFV), “position index” (PI) and “orientation index” (OI) were provided to assess involuntary movements due to muscular weakness.

Results: 33 patients with CIDP and 28 HC were included. All measures were significantly elevated in CIDP patients for both devices in the right and left hand compared to healthy controls. Subgroup analysis revealed no differences between typical and atypical CIDP variants. INCAT score only weakly correlated with OI and PI. However, there was a stronger correlation between MRC and QIMA parameters in both hands.

Conclusion: Q-Motor assessments were capable to objectively assess muscular weakness in CIDP. In particular, QIMA measures detected subclinical generalized muscle weakness even in patients with milder disability. Sensitivity and rater-independence of Q-Motor assessments support a further exploration of QIMA measures as potential endpoints for future clinical trials in CIDP.

Keywords: CIDP, Clinical outcome parameter, CIDP subgroups, Case control studies, Diagnostic test assessment
Background
Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare autoimmune disorder of the peripheral nervous system leading to both proximal and distal weakness of all extremities. Beside this typical manifestation, there is a proportion of patients suffering from atypical variants such as pure sensory (sensory CIDP), distally acquired demyelinating polyneuropathy (DADS) or asymmetric multifocal acquired demyelinating sensory and motor polyneuropathy (MADSAM) neuropathies [1, 2]. CIDP is a demyelinating disease leading to typical demyelinating changes, which can be detected by nerve conduction studies according to different established demyelinating criteria (European Federation of Neurological Societies, EFNS; American Academy of Neurology, AAN) and by MR-neurography or ultrasound. However, diagnosis may still be challenging due to the fact that CIDP patients can be objectively quantified with (1) non-invasive Q-Motor assessment of grip force and involuntary activity and (2) that pathological findings correlate with disease severity as measured by the MRC and INCAT disability score. In these cases, established paraclinical criteria may not be sufficient alone. Accordingly, there is a remarkable rate of misdiagnosed CIDP, mainly atypical CIDP [4]. Recent studies revealed the presence of autoantibodies to paranodal junction proteins, such as neurofascin 155 and contactin 1 in a subpopulation of CIDP patients [5]. There is evidence that the underlying mechanism is distinct from those with classical macrophage-induced demyelination [6].

Besides diagnostic challenges, the assessment of muscular weakness is the most important treatment outcome parameter. Based on recent studies there is an increasing need to objectively assess the treatment efficacy in order to avoid overtreatment and reduce high treatment costs such as by intravenous immunoglobulins (IVIG). The Medical Research Council Sum Score is often applied in order to measure the muscle strength on the level of impairment [7], whereas the INCAT overall disability scale measures the disability resulting from muscular weakness [8]. However, none of these methods is appropriate to assess muscle weakness objectively and to detect even very small subclinical changes.

Here, we hypothesized that muscular weakness in patients with CIDP can be objectively quantified with (1) non-invasive quantitative motor (Q-Motor) assessment of grip force and involuntary activity and (2) that pathological findings correlate with disease severity as measured by the MRC and INCAT disability score. In addition, we asked whether patients with atypical manifestation show subclinical signs of generalized muscle weakness compared to healthy controls.

Methods
Patients
In this cross-sectional observational study patients who met the diagnostic criteria for typical and atypical CIDP of the EFNS 2010 [9] were included in order to objectively quantify muscular weakness with non-invasive Q-Motor assessment of grip force and involuntary activity. Patients were screened consecutively between March and August 2013 in our outpatient clinic of the Department of Neurology, Charité University Medicine, Berlin, Germany. Data of all CIDP patients was compared to a group of healthy controls (HC) that was similar in age and sex (distribution) to the patient group. HC had to meet the following criteria: Age ≥ 18 years, no other neurological diseases, no other diseases affecting the musculoskeletal system, no cognitive deficits. Overall, 33 patients with CIDP and 28 HC were included. Unlike recent epidemiological data, numbers of recruited typical and atypical CIDP patients were nearly identical for statistical reasons [10]. There was no testing for NF155 and CNTN1 antibodies for patients with atypical CIDP.

Clinical assessment
Patients were examined by the treating neurologist (JK). Sociodemographics as well as current medication were documented. We used the adjusted inflammatory neuropathy cause and treatment (INCAT) disability score [8] and the Medical Research Council (MRC) sum score [7] to assess the clinical status within 2 months when clinically stable. For the MRC the following muscles had been tested on both sides: shoulder abduction, elbow flexion, wrist extension, index finger extension, hip flexion, knee extension, ankle dorsiflexion, extension of the big toe. For classification, we used CIDP disease activity status (CDAS) [11], summarizing unstable active and improving status as unstable stage, stable active status and remission status as stable stage..

Quantitative motor assessment and data analysis
The Quantitative-Motor (Q-Motor) grip-and-lift task (manumotography) providing data for “Quantitative Grip Force Assessment” (QGFA) and “Quantitative Involuntary Movement Assessment” (QIMA) was performed as described earlier [12, 13]. Briefly, all subjects were seated in an upright position. They were then asked to grip and lift an instrument with two force-torque sensors (Nano-40, ATI, Apex, NC), which measured the grip (normal) and load (tangential) forces of the thumb and index finger. The instrument’s weight could be modified to 250 g (light) and 500 g (heavy). An electromagnetic sensor (Fastrack, Polhemus, VT)
constantly measured the instrument’s three-dimensional position \((x, y, z)\) and orientation \((roll, pitch, yaw)\). The object was held 10 cm adjacent to a marker for 15 s (static holding phase). Patients performed five consecutive recorded trials with each object weight (light and heavy) and with both hands.

The mean isometric grip force (GF) was calculated as the average of the 5 repetitions during the static holding phase. The amount of involuntary movement during the static holding phase was assessed by recording changes in position \((x, y, z)\) and orientation \((roll, pitch, yaw)\). In order to assess the mean amount of involuntary movements during the static phase, the means of the absolute values of the derivatives of position \((the \, x, \, y, \, and \, z \, channels)\) and of the orientation \((roll, pitch, \, and \, yaw \, channels)\) were calculated and summed up to create a position index \((PI)\) and an orientation index \((OI)\) [14]. For patients who were treated with infusions on a regular basis, Q-Motor tests were obtained in the middle of an infusion interval in order to avoid end of dose effects.

All Q-Motor data was transferred to the Q-Motor group at the George-Huntington-Institute, Muenster, Germany, for blinded quality control and automated computerized data analysis. Q-Motor outcomes were then returned to the Charité for further analysis.

**Statistical analysis**

Statistical analyses were performed using Prism 6 software (GraphPad, La Jolla, CA, USA). For group differences with regard to sex and treatment history Fisher’s exact test was used. For normally distributed age, MRC and INCAT score, unpaired t-test was used. QGFA and QIMA parameters were tested by the two-tailed Mann-Whitney and Kruskal-Wallis tests followed by Dunn’s multiple comparison tests in two and more groups, respectively. Level of significance was defined as \(p < 0.05\) for all comparative tests. We did not perform corrections for multiple comparisons as this was an exploratory study to explore proof-of-concept for quantitative measurements for future research. To detect associations among Q-Motor measures \((GF, PI, OI)\) and disease severity as measured by the MRC-A score and INCAT ODSS, we calculated Spearman coefficients.

**Results**

**Patient characteristics**

Altogether 33 CIDP patients were included, of these 22 (66.7%) fulfilled EFNS criteria of definite CIDP, 10 (30.3%) patients of probable CIDP and one patient with possible CIDP (3%). Mean age was 64 years (median 65, 44–82) with no significant difference to control group with a mean age of 59 years (median 60, 37–77). There was a huge range regarding disease duration with a minimum of one year and a maximum of 28 years (Median 5, IQR 2–8). CIDP patients and controls did not differ in sex, however atypical and typical patients differed in sex significantly (see Table 1). 16 patients suffered from typical CIDP (48.5%), and 17 patients from atypical variants (51.5%). Of those with atypical variants, 10 patients suffered from DADS, 4 patients of sensory CIDP and 3 of MADSAM (see Table 1). Patients with typical CIDP had a higher INCAT ODSS compared to atypical CIDP \((p = 0.0004)\), which was also confirmed for INCAT-A (INCAT Score of the arms) \((p = 0.003)\). Mean MRC–sum Score was 71.3 (SD 7.5; Minimum 48, Maximum 80). However, MRC was only obtained from 22 patients. At the time of assessment, 19 (57.6%) patients had been treated with IVIG, 7 (21%) with glucocorticosteroids, none with plasma exchange (PE), 5 (15%) with other immunosuppressants (methotrexate, azathioprine) and two received no treatment. The majority of patients had been treated with glucocorticosteroids sometime before. Only about 24% received plasma exchange in history. There was no difference between typical and atypical CIDP in terms of treatment procedures (Table 1).

**Quantitative grip force and involuntary movement assessment in CIDP versus controls**

The Q-Motor measures position index \((PI)\), orientation index \((OI)\), and grip force variability \((GFV)\) were significantly increased in all CIDP patients compared to HC for both weights in the left and also in the right hand (Table 2, shown here only data for 500 g). No differences between CIDP patients and HC were found for isometric grip force (for details see Table 2).

**Subgroups analysis of atypical versus typical CIDP**

There was a statistical difference between typical, atypical CIDP and HC for the position index \((PI)\) as well as for orientation index \((OI)\) (Kruskal-Wallis-test \(p < 0.001\)). In post hoc analysis, PI as well as OI differed significantly between typical or atypical and HC for both weight classes. However, no statistical difference could be detected between typical and atypical groups itself in post hoc analysis (Table 3). Grip force variability differed between CIDP subgroups and HC for both weight classes with no difference between typical and atypical CIDP in post hoc analysis (Table 3 for 500 g, data not shown for 250 g). Patients with only very mild affection of the arm function \((INCAT-A \leq 1, n = 11 [36.7%]) as well as patients with higher arm function disability \((INCAT-A \geq 2, n = 21 [63.3%]) showed significantly higher values for the PI as well as for OI for both hands and weights compared to HC. For grip force variability, only patients with INCAT-A \(\geq 2\) showed significant increased values compared to HC (Table 4 for 500 g, data not shown for 250 g).
Correlation with INCAT ODSS and MRC

For all parameters that were significantly increased in CIDP patients, we assessed the correlation with the INCAT and MRC score. There was a weak correlation of GFV right hand 250 g of all CIDP patients with INCAT score (Fig. 1a, Spearman correlation index $r = 0.37$, $p = 0.047$) but not with MRC (data not shown). OI of both hands correlated by trend with INCAT (Fig. 1b shows for the right hand, Spearman correlation index $r = 0.37$, $p = 0.05$). There was also a moderate correlation of OI with MRC-A of both hands for 500 g ($r = -0.47$, $p = 0.03$). There was no correlation of PI with INCAT or INCAT-A (data not shown). However, we found a moderate correlation of PI with MRC-A for the both hands (Fig. 1d shows for 250 g right hand, for the left hand $r = -0.46$, $p = 0.04$; 500 g $r = -0.47$, $p = 0.03$).

Discussion

In this cross-sectional pilot study we investigated 33 CIDP patients compared to 28 HC using the Q-Motor grip-and-lift task quantitatively assessing grip force and involuntary movements. Aim of the study was to objectively assess muscle weakness and to detect even very small subclinical changes in CIDP patients as well as to search for differences between typical and atypical CIDP variants. Involuntary movements parameters such as

### Table 1 Patient characteristics

|                      | CIDP all | Typical CIDP | Atypical CIDP | HC  |
|----------------------|----------|--------------|---------------|-----|
| N total              | 33       | 16           | 17            | 28  |
| sex, female (%)      | 12 (36.4)| 10 (62.5)    | 2 (11.76)     | 14  (50) |
| age (years), mean (SD)| 64.18 (9.94) | 62.50 (11.65) | 65.75 (8.04) | 59.54 (8.94) |
| medium (range)       | 65 (44–82) | 61 (44–82)   | 68 (52–80)   | 60  (37–77) |
| time since diagnosis, years, median (IQR) | 5 (2–8) | 7.5 (2.75–14.25) | 3 (2–7) | n.a. |
| INCAT ODSS, mean (SD) | 3.4 (1.6) | 4.4 (1.5)    | 2.4 (1.0)    | n.a. |
| - arms               | 1.4 (0.75) | 2.4 (1.0)    | 1.4 (0.96)   | n.a. |
| - legs               | 1.5 (0.9) | 2 (1.0)      | 1.0 (0.001)  | n.a. |
| MRC, mean (SD)       | 71.5 (7.5) | 68.9 (9.9)   | 73.0 (5.1)   | n.a. |
| treatment actually/ever (%) | 7/24 (21/72.8) | 5/13 (31/81) | 2/11 (12/64) | n.a. |
| - glucosteroids      | 19/33 (58/100) | 10/16 (63/100) | 9/17 (53/100) | n.a. |
| - IVIg               | 0/8 (0/24.2) | 0/4 (0/25)   | 0/4 (0/23)   | n.a. |
| - PE                | 5/7 (15/21) | 3/5 (19/31)  | 2/2 (12/12)  | n.a. |

* missing data of one patient regarding handedness in CIDP group

Abbreviations: INCAT Inflammatory Neuropathy Cause and Treatment disability score, MRC Medical Research Council, SD Standard deviation, IQR Interquartile range, IVIg Intravenous immunoglobulin, PE Plasma exchange

### Table 2 QGFA and QIMA parameters in CIDP versus controls

| Q-Motor measure (unit) | CIDP | HC | p-value | n CIDP/HC |
|------------------------|------|----|---------|-----------|
| Mean isometric grip force 500g, left hand (N) | 10.86 (4.24) | 9.1 (2.95) | 0.1733 | 32/27 |
| Mean isometric grip force 500g, right hand (N) | 10.55 (3.95) | 10.38 (4.05) | 0.8881 | 31/28 |
| Grip force variability 500g, left hand (%) | 6.97 (2.34) | 5.40 (1.79) | 0.0091 | 32/27 |
| Grip force variability 500g, right hand (%) | 6.36 (1.96) | 5.4 (2.38) | 0.0085 | 31/28 |
| Orientation index 500g, left hand (°/s) | 11.15 (6.09) | 5.31 (4.13) | < 0.0001 | 30/26 |
| Orientation index 500g, right hand (°/s) | 12.19 (7.74) | 5.17 (3.36) | < 0.0001 | 30/27 |
| Position index 500g, left hand (cm/s) | 3.50 (1.51) | 1.56 (0.83) | < 0.0001 | 30/26 |
| Position index 500g, right hand (cm/s) | 3.49 (1.65) | 1.84 (1.47) | < 0.0001 | 30/27 |
### Table 3 Subgroup analyses of typical and atypical CIDP

| Parameter (Unit) | Typical CIDP | Atypical CIDP | HC | p-value | Post hoc* | No.** |
|------------------|--------------|---------------|----|---------|----------|------|
| Mean isometric grip force 500g_ left hand (N) | 9.34 (3.19) | 12.20 (4.67) | 9.1 (2.95) | 0.0777 | a) ns | 15/17/27 |
| Mean isometric grip force 500g_ right hand (N) | 9.40 (3.93) | 11.70 (3.73) | 10.38 (4.05) | 0.1681 | a) ns | 16/16/28 |
| Grip force variability 500g_ left hand (%) | 6.94 (2.56) | 6.99 (2.20) | 5.40 (1.79) | 0.0319 | a) ns | 15/17/27 |
| Grip force variability 500g_ right hand (%) | 7.16 (2.11) | 5.56 (1.46) | 5.4 (2.38) | 0.0043 | a) ** | 16/16/28 |
| Orientation index 500g_ left hand (°/s) | 13.24 (7.38) | 9.54 (4.47) | 5.31 (4.13) | < 0.0001 | a) *** | 13/17/26 |
| Orientation index 500g_ right hand (°/s) | 13.45 (6.37) | 11.08 (8.82) | 5.17 (3.36) | < 0.0001 | a) *** | 14/16/27 |
| Position index 500g_ left hand (cm/s) | 3.43 (1.35) | 3.59 (1.65) | 1.56 (0.83) | < 0.0001 | a) *** | 10/19/26 |
| Position index 500g_ right hand (cm/s) | 3.20 (1.91) | 3.68 (1.56) | 1.84 (1.47) | < 0.0001 | a) ** | 10/19/27 |

* a) Typical CIDP vs. HC, b) Atypical CIDP vs. HC, c) Typical CIDP vs. Atypical CIDP  
** typical/atypical/HC

### Table 4 Subgroup analyses of mild and higher function disability

| Parameter (Einheit) | INCAT-A ≤ 1 | INCAT-A ≥ 2 | HC | p-value | Post hoc* | No.** |
|---------------------|-------------|-------------|----|---------|----------|------|
| Mean isometric grip force 500g_ left hand (N) | 11.44 (4.64) | 10.64 (4.18) | 9.1 (2.95) | 0.3487 | a) ns | 11/20/27 |
| Mean isometric grip force 500g_ right hand (N) | 10.28 (2.47) | 10.77 (4.69) | 10.38 (4.05) | 0.9712 | a) ns | 11/20/28 |
| Grip force variability 500g_ left hand (%) | 6.55 (2.18) | 7.27 (2.47) | 5.40 (1.79) | 0.0223 | a) ns | 11/20/27 |
| Grip force variability 500g_ right hand (%) | 5.97 (2.35) | 6.63 (1.77) | 5.4 (2.38) | 0.0123 | a) ns | 11/20/28 |
| Orientation index 500g_ left hand (°/s) | 10.24 (4.02) | 11.78 (7.08) | 5.31 (4.13) | < 0.0001 | a) ** | 10/19/26 |
| Orientation index 500g_ right hand (°/s) | 10.46 (9.32) | 13.17 (7.09) | 5.17 (3.36) | < 0.0001 | a) ** | 10/19/27 |
| Position index 500g_ left hand (cm/s) | 3.43 (1.35) | 3.59 (1.65) | 1.56 (0.83) | < 0.0001 | a) *** | 10/19/26 |
| Position index 500g_ right hand (cm/s) | 3.20 (1.91) | 3.68 (1.56) | 1.84 (1.47) | < 0.0001 | a) ** | 10/19/27 |

* a) INCAT ≤ 1 vs. HC, b) INCAT ≥ 2 vs. HC, c) INCAT ≤ 1 vs. INCAT ≥ 2  
** INCAT-A ≤ 1/ INCAT ≥ 2/ HC
GFV, OI and PI were significantly elevated in CIDP compared to HC. Subgroup analysis revealed no difference between typical and atypical CIDP groups itself. Interestingly, patients with only very mild affection of the arms (INCAT-A ≤ 1) showed the same alterations of OI and PI compared to more disabled patients (INCAT-A ≥ 2).

Beside sensory disturbance, the assessment of muscular weakness is essential in order to establish diagnosis as well as evaluate treatment outcome.

So far, MRC and Martin’s Vigorimeter are established endpoints applied in clinical routine. Grip strength can be measured by using the Vigorimeter, a simple objective tool that is easy to apply [15, 16]. However, it is only a one-dimensional tool and thus may not be sensitive enough to measure small subclinical changes in manual coordination, for instance at disease onset or in atypical variants.

The medical research council scale (MRC) also works on the impairment level but has a great interrater variability and thus inherited imprecision. As a third outcome measure, the INCAT disability scale assesses disabling problems in daily arm and leg mobility and has evolved as the most established primary outcome in clinical trials since it was used in the large ICE trial of CIDP patients [17, 18]. However, it mainly detects actual disability and by definition is not sensitive to detect smaller alterations.

The quantitative Q-Motor assessments were shown to detect subclinical changes in patients with premanifest Huntington’s disease and correlated well with disease severity [13, 14, 19] and progression even 2 decades before
published studies [16, 18] when using the INCAT score groups, no differentiation has been performed in clinical picture differs markedly between CIDP subgroups. This would need further confirmatory studies. MRC has been obtained only from 22 patients. However, despite the limited number of MRC measurements, correlation with QIMA parameters reached statistically significance. In addition, grip strength parameters by Martin vigorimeter or Jamar [16, 26] have not been obtained and should be included in a further larger cohort trial.

Recently, Knak et al. showed that grip strength is less responsive to detect improvements after treatment than isokinetic dynamometry at ankles in a retrospective study. The authors concluded that grip strength as measured by JAMAR dynamometer does not seem to be an appropriate surrogate parameter of overall muscle strength and should be combined with isokinetic measurements of the lower limbs [27]. In the present study, we did not search for treatment efficacy parameters. However, in order to obtain appropriate overall muscle strength additional strength parameters of the lower limbs such as isokinetic measurements or foot tapping by Q-Motor may have to be amended. Furthermore, we did not perform corrections for multiple comparisons, as this was an exploratory proof-of-concept study. However, the changes in OI and PI were robust and consistent, supporting a likely biological relevance of our findings. In addition, almost all patients had a stable disease activity status, i.e. they were stable under treatment or in remission. Measuring treatment naïve patients in future CIDP trials may be useful to objectively assess muscular weakness in CIDP. The observations of our study encourage further exploration in larger cohort trials. In particular, QIMA parameters seem to be suitable to detect subclinical generalized muscle weakness in patients with milder disability and/or atypical phenotype. Therefore, they might be a sensitive and reliable endpoint in future CIDP trials and support data-driven, unbiased decision making in clinical development of novel therapies.

Conclusions
Q-Motor tests may be useful to objectively assess muscular weakness in CIDP. The observations of our study encourage further exploration in larger cohort trials. In particular, QIMA parameters seem to be suitable to detect subclinical generalized muscle weakness in patients with milder disability and/or atypical phenotype. Therefore, they might be a sensitive and reliable endpoint in future CIDP trials and support data-driven, unbiased decision making in clinical development of novel therapies.

Abbreviations
AAN: American Academy of Neurology; CDAS: Clinical disease activity score; CIDP: Chronic inflammatory demyelinating polyneuropathy; DADS: Distal acquired demyelinating polyneuropathy; EFNS: European Federation of Neurological Societies; GF: Grip force; GFV: Grip force variability; HC: Healthy control; INCAT: Inflammatory neuropathy cause and treatment; IQR: Interquartile range; IVIg: Intravenous immunoglobulin; MADSAM: Multifocal acquired demyelinating sensory and motor polyneuropathy; MRC: Medical Research Council scale; PI: Orientation index; PI: Position index; QGFA: Grip Force Assessment; QIMA: Involuntary Movement Assessment; Q-Motor: Quantitative motor test; SD: Standard deviation

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Authors’ contributions
All authors read and approved the final version of the manuscript and gave consent for publication. JK: Design and conceptualization of the study, acquisition of data, statistical analysis and interpretation of data, drafting of manuscript; accountable for all aspects of the manuscript. SB: Acquisition of data, statistical analysis of data, interpretation of data, revision of manuscript for intellectual content. MD: Acquisition of data, revision of manuscript for intellectual content. SH: Interpretation of data, revision of manuscript for intellectual content. AJB: Interpretation of data, revision of manuscript for intellectual content. FP: Interpretation of data, revision of manuscript for intellectual content. RR: Design and conceptualization of the study, interpretation of data, revision of manuscript for intellectual content. AM: Interpretation of data, revision of manuscript for intellectual content.
Acquisition of data, interpretation of data, revision of manuscript for intellectual content, final approval of the published manuscript version.

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Availability of data and materials
The datasets analysed and used during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was approved by the ethics committee of the Charité – Universitätsmedizin Berlin (EA1/025/11). All patients gave written informed consent in accordance with the Declaration of Helsinki in its currently applicable form. This consent was signed by the patient if possible, or by a third person in the presence of the full conscious patient. These criteria were approved by the ethics committee. Any patient in this study was able to provide written informed consent due their condition.

Consent for publication
Not applicable.

Competing interests
J Klehmet received speaker’s honoraria and travel grants from Griffols, Octapharma, CSL Behring, Novartis, Bayer and Merck, S Beutner, S Helfmann, M Dornauer, and A Meisel declare no competing interests. F Paul serves on the scientific advisory board for Novartis; received speaker honoraria and travel funding from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, Medimmune, and Shire; is an academic editor for PLoS ONE; is an associate editor for Neurology® Neuroimmunology & Neuroinflammation; consulted for Sanofi/Genzyme, Biogen Idec, Medimmune, Shire, and Alexion; and received research support from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/ Genzyme, Alexion, Merck Serono, German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research, Arthur Arnstein Stiftung Berlin, EU FP7 Framework Program, Arthur Arnstein Foundation Berlin, Guthy Jackson Charitable Foundation, and National Multiple Sclerosis of the USA. R Reilmann is founding director and owner of the George-Huntington-Institute, a private research institute focused on clinical and preclinical research in Huntington’s disease, and Quantimedias, a clinical research organization providing Q-Motor (quantitative motor) services in clinical trials and research. He holds appointments at the Dept. of Radiology of the University of Muenster and at the Department of Neurodegenerative Diseases and Hertie-Institute for Clinical Brain Research, University of Tuebingen. Dr. Reilmann serves as elected member of the Steering Committees of the European Huntington Disease Network (EHDN) and the Huntington Study Group (HSG), co-chair of the Task Force on Huntington’s disease and member of the Task Force on Technology of the International Parkinson and Movement Disorder Society (IPMDS). He has provided consulting services, advisory board functions, clinical trial services, quantitative motor analyses, and/or lectures for Actelion Pharmaceuticals, Armin Neuroscience, AOP Orphan Pharmaceuticals, Cure Huntington Disease Initiative Foundation (CHDI), Desert, Hoffmann-La Roche, IONIS Pharmaceuticals, Ipsen, Lundbeck, Link Medicine, MEDA Pharma, Medivation, Mitoxonix, Neurosearch, Novartis AG, Omeros, Pfizer, Prana Biotechnology, Prionlica, Raptor Pharmaceuticals, Siena Biotech, Templer Pharma, Teva Pharmaceuticals, uniQure, Vaccinex, Wave Life Sciences, and Wyeth Pharmaceuticals. He has received grant support from the Bundesministerium für Bildung und Forschung (BMBF), the Cure Huntington Disease Initiative Foundation (CHDI), the Deutsche Forschungsgemeinschaft (DFG), the Deutsches Zentrum für Neurodegeneration und Entzündung (DZNE), the European Union 7th Framework Program (EU-FP7), the European Huntington Disease Network (EHDN), the High-Q-Foundation, and the National Science Foundation (NSF). A U Brandt is cofounder and shareholder of technology companies Motognosis GmbH and Nocturne GmbH. He is named as inventor on several patent applications describing serum biomarkers in multiple sclerosis, perceptive visual computing based motion analysis and retinal image analysis.

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