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Original article

Postural balance and visual dependence in patients with demyelinating neuropathies differ between acquired and hereditary etiologies

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ABSTRACT

Background. – Demyelinating polyneuropathies affect posture and can be either hereditary, as in Charcot-Marie-Tooth type 1A (CMT1A), or autoimmune, as in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Clinical differentiation between these two neuropathies can be challenging and biomarkers are lacking. No comparative analysis of their balance profiles has been conducted.

Methods. – The postural balance of 23 patients with CIDP and 23 patients with CMT1A, matched for age, sex, and functional scores, were recorded using a force platform under various conditions. The effects of visual dependence were examined based on center of pressure velocity, 90% confidence ellipse area, and the Romberg quotient which represents the ratio between posturography with eyes closed and eyes open.

Results. – With eyes open, the two groups exhibited similar area and velocity. They increased their postural sway when visual input was eliminated. Nevertheless, the increase in postural sway was less pronounced in CMT1A patients than in patients with CIDP, who then had a higher Romberg quotient.

Conclusion. – Patients with CMT1A appear to have developed compensatory mechanisms over time resulting in reduced visual dependence. Further studies are necessary to explore other compensatory mechanisms of equilibrium that could be targeted by rehabilitation for patients with CIDP.

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Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMT1A, Charcot-Marie-Tooth 1A; CMT, Charcot-Marie-Tooth; CoP, center of pressure; EDX, electrodiagnostic; INCA, inflammatory neuropathy cause and treatment disability score; IVIg, intravenous immunoglobulin; MRC, Medical Research Council; NCV, nerve conduction velocity; ONLS, overall neuropathy limitations scale; RODS, rasch-built overall disability scale; RQ, Romberg quotient.

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1. Introduction

Among demyelinating neuropathies, some are acquired while others have a hereditary nature. One of the rare forms of acquired autoimmune neuropathies is chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), which, in its typical form, manifests as a symmetrical motor/sensory disorder with both proximal and distal muscle weakness. Impairment of proprioception and balance disturbances are common clinical features in patients with CIDP [1].

Charcot-Marie-Tooth disease (CMT), and more specifically, CMT type 1A, is the most common rare hereditary neuropathy [2,3]. In its classic form, CMT1A is characterized by symmetrical and progressive distal muscle weakness, loss of sensation, and musculoskeletal deformities in the feet [4]. Poor balance and postural instability are also often clinically observed in individuals with CMT1A [5,6].

While the classification between hereditary and acquired neuropathy is often straightforward, errors in diagnosis can occur in the presence of atypical characteristics or sporadic neuropathy [7,8], even in expert centers [9]. Subjective clinical observation of the postural balance of patients with rare demyelinating neuropathies can help guide the diagnosis. Based on the experience of neurologists, patients with hereditary neuropathy seem to have less impairment (patients are said to be “less impaired than their electrodiagnostic [EDX]”), balance usually being evaluated with the Romberg maneuver (worsening of the proprioceptive ataxia when eyes closed). However, this better balance in CMT patients (than in CIDP) has never been evaluated systematically. It is supposedly related to the chronic (neurodevelopmental) pathophysiology of CMT and may give us some clues both for a better diagnostic classification and also for rehabilitation of CIDP patients by proposing compensatory mechanisms.

A quantitative assessment of postural balance is possible through the analysis of static postural sway (posturography), examining the trajectory of the center of pressure (CoP) [10]. The CoP, which is the barycenter of the vertical reaction forces distributed over the entire foot-floor contact surface, moves unconsciously when the subject tries to maintain a position. This movement results in a trajectory, an area, and a swaying velocity [11]. Postural balance integrates visual, proprioceptive, and vestibular systems in a dynamic way, with different steps from afferences, perception, and correction of disequilibrium.

The primary objective of the study was to determine if patients with CIDP exhibit a more severe proprioceptive ataxia (evaluated with a quantitative Romberg quotient [RQ]) than patients with CMT1A. The secondary objective was to explore the strategy of postural balance and the visual dependency in these two neuropathy groups.

2. Material and methods

This was a single-center (regional, reference center for neuromuscular diseases) prospective comparative study.

2.1. Patient selection

Due to the rarity of these neuromuscular pathologies, all patients followed in the center’s active registry who provided consent were recruited, and age-sex matching was performed post-hoc. This prospective study lasted one year.

Twenty-three patients with CMT1A (13 females; age: 57.0 [50.5–68.0]) and 23 patients with CIDP (9 females; age: 51.0 [49.0–57.0]) participated in the study. All patients had a confirmed diagnosis of neuropathy with clinical lower limb symptoms; respectively, they met the criteria of the European Federation of Neurological Societies/Peripheral Nerve Society Guideline [12] for typical CIDP (CIDP group) and had a positive genetic analysis for the duplication of the *PMP22* gene (CMT1A group). Patients with neurological history other than neuropathy (such as epilepsy, stroke, dementia) or significant musculoskeletal conditions (severe foot deformities or severe scoliosis) that could impact balance were not included. Due to the risk of falls and safety, patients who were unable to maintain the Romberg test were not included in this study. All included CIDP patients were stable under intravenous immunoglobulin (IVIg) therapy, and the assessments were conducted at the end of the treatment cycle, on the day of administration. Regarding the CIDP group, data on disease duration and nerve conduction velocity (NCV) evaluations were collected. For the CMT1A patients, EDX data were missing due to examinations being conducted during childhood and the early abolition of sensory potentials (and also abolished motor potentials in lower limbs). The precise NCV data are presented in the supplementary material.

2.2. Clinical assessments

The forty-six subjects underwent a clinical assessment, including

- Romberg test [13]: Mariette’s score to evaluate ataxia ranging from 0, normal, to 3, severe ataxia. A score of 1 corresponds to mild oscillations, 2 to moderate oscillations, and 3 to severe oscillations;
- Muscle testing (MRC [14,15]): score ranging from 0, no contraction, to 5, normal contraction for lower limb muscles: hip flexors, knee flexors, ankle flexors and extensors;
- Clinical evaluation of sensory modalities of the lower limb (INCAT [16]) score ranging from 0, normal, to 8, abnormal at the hip;
- Global disability scale (RODS [17]) ranging from 0, total limitation, to 48, no limitation;
- Overall neuropathy limitations scale (ONLS [18]) ranging from 0, no limitation, to 12, severe disability: obtained by summing between ONLS score for the upper limb (/5) and the lower limb (/7).

The study was conducted in accordance with the Declaration of Helsinki and approved by the independent local ethics committee (CPP Île-de-France 11, Reference 18,039, registration number: 2017-A02861-52, NCT04154540), and all subjects provided written consent.

2.3. Experimental setup and data analysis

The patients were instructed to stand for 60 seconds on a force platform, with feet parallel and together, looking straight ahead with arms by their sides, miming the clinical Romberg test. Two conditions were performed: eyes opened and eyes closed. All tests were conducted in the same order and without shoes. The variations in the CoP position were recorded for 60 seconds using a force platform (the ORG-5 model from AMTI®, Watertown, MA, USA), and the output data were sampled at 1000 Hz.

The data for mean velocity (velocity in mm/s), the area of the 90% confidence ellipse (area in mm²), anteroposterior and mediolateral sway (in mm) were then calculated using an in-house MATLAB® script (The MathWorks, Natick, MA, USA).

To investigate the mechanisms of postural control, we chose a criterion closely related to the clinical qualification of proprioceptive ataxia: the posturographic Romberg quotient (RQ-area), which is a ratio between 90% confidence ellipse area with eyes open and 90% confidence ellipse area with eyes closed [19,20]. The same ratio was used for velocity (RQ-velocity).

2.4. Falls

A fall was considered when the assessor had to catch or assist the participant to prevent an actual fall or for any attempts interrupted before the end of the test. If the patient did not maintain the starting position, the trial was also considered as a fall.

2.5. Statistical analysis

The data analysis was conducted using SPSS v.26.0 (SPSS Statistics, Armonk, NY: IBM Corp) and R Statistical Software (version 4.3.3; R Foundation for Statistical Computing). Non-

parametric statistics were favored following the normality analysis. A Mann-Whitney test was employed to compare anthropometrics, clinical data and RQ (area and velocity), between the CIDP and CMT1A groups. To compare area, sway, and velocity of the CIDP and CMT1A groups, a mixed-effects model was used. Due to the non-parametric nature of the data, a logarithmic transformation was applied to meet the analysis conditions required by the mixed-effects model. For post-hoc comparisons between the two groups and the two conditions, Tukey tests were conducted to identify significant between group differences. A significance threshold of 0.05 was applied to all analyses. The effect of the interaction between condition and groups was examined using the Hedge's *g* effect size calculation. Effect sizes were categorized as large if 0.8 or over, moderate if 0.5 to 0.79 and small if 0.49 or less. For categorical variables (sex ratio and falls), a Chi-square test was used, as appropriate.

3. Results

Anthropometrics and clinical examination data were similar between groups, namely sensory-motor scores did not differ between groups (Table 1). For the CIDP patients, the median [Q1–Q3] disease duration since first perceive symptom was 6.5 [5.0–11.0] years and 27 [11.5–39] for the CMT1A group. In the CIDP group, 10 (43.5%) exhibited conduction blocks in the NCV tests, and 10 patients (43.5%) showed secondary axonal loss, whereas CMT1A group showed 0 conduction block and 19 secondary axonal losses (3 missing data) (Supplementary Data Table 1). In the CMT1A group, the global nerve deficit showed a more significant secondary motor and sensory axonal loss compared to the CIDP group (Supplementary Data Table 2).

RQ-Area and RQ-velocity showed higher ratios in CIDP compared to CMT1A (Fig. 1), with moderate ($g = 0.70$) and large effects ($g = 0.83$) respectively for these two ratios (Table 2).

Table 1 – Anthropometric, and clinical data for the CIDP and CMT1A groups.

	CIDP	CMT1A	P-value
	(n = 23)	(n = 23)	
	Median [Q1–Q3]	Median [Q1–Q3]	
Anthropometric data			
Age (years)	57.0 [50.5–68.0]	51.0 [49.0–57.0]	0.080
Sex (F/M)	10/13	14/9	0.248
BMI (kg/m ²)	26.0 [23.1–30.5]	25.0 [23.2–28.5]	0.510
Disease duration since first perceived symptom	6.5 [5.0–11.0]	27.0 [11.5–39.0]	< 0.001
Clinical data			
MRC score (/40)	37.5 [31.5–40.0]	36.5 [34.0–38]	0.731
MRC tibial score (/10)	8.0 [6.3–10.0]	8.0 [6.0–8.0]	0.271
INCAT sensory score (/8)	2.0 [1.3–4.0]	3.5 [2.0–6.0]	0.248
Ataxia (/3)	1.0 [1.0–2.0]	1.0 [1.0–1.0]	0.093
ONLS – lower limbs (/7)	1.0 [1.0–2.0]	2.0 [1.0–2.0]	0.199
ONLS upper limb (/5)	1.0 [0.0–2.0]	1.0 [0.0–2.0]	0.411
ONLS - total (/12)	2 [1.0–4.0]	2.5 [2.0–3.0]	0.881
RODS (/48)	39.0 [33.5–44.5]	38.0 [35.0–40.8]	0.586

MRC: Medical Research Council scale; INCAT: sensory score; ONLS: overall neuropathy limitations scale; RODS: rasch-built overall disability scale; NA: non-applicable. Median values with interquartile ranges (Q1–Q3) for continuous variables and counts for categorical variables. P-values, evaluated by Mann-Whitney test, indicate the significance of differences between the two groups.

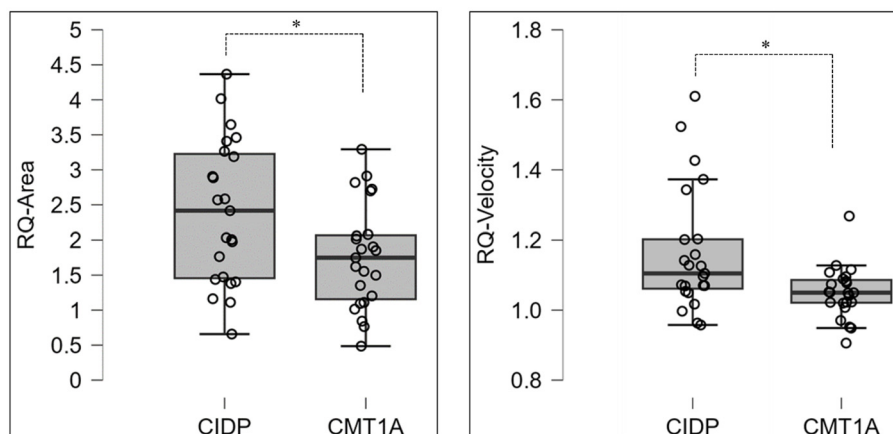


Fig. 1 – Descriptive box plots of Romberg Quotient for area and velocity. RQ shows higher ratios in CIDP compared to CMT1A. RQ: Romberg Quotient. *P-values < 0.05, evaluated by Mann-Whitney test.

Table 2 – Romberg quotient in the CIDP and CMT1A groups.

	CIDP	CMT1A	Mann-Whitney	
	Median [Q1–Q3]	Median [Q1–Q3]	P-value	Hedge's g
RQ-Area	2.42 [1.46–3.23]	1.75 [1.16–2.07]	0.040*	0.696
RQ-Velocity	1.11 [1.06–1.20]	1.05 [1.02–1.09]	0.011*	0.825

Median values with interquartile ranges (Q1–Q3) for continuous variables. RQ: Romberg quotient. *P-values < 0.05, evaluated by Mann-Whitney test, indicate the significance of the effect of group (CIDP vs. CMT1A).

In the open eyes condition (Table 3), analyzed variables did not differ between groups.

Without vision (Fig. 2-B), area was higher for the CIDP group (1082.0 mm² [846.5–2453.0]) compared to the CMT1A group (840.0 mm² [537.5–1101.5]). Velocity did not show any difference between groups (Table 3). However, mediolateral sways were greater in the CIDP group ($P = 0.020$) without difference for anteroposterior between the two groups ($P = 0.091$).

In both populations, the absence of vision increased area and sway (Fig. 2). Velocity of the CoP displacement increased in the CIDP group but did not differ in the CMT1A group (Fig. 2-A).

No falls occurred in any of the groups/conditions.

4. Discussion

4.1. Posturographic Romberg quotient

In this study, we demonstrated, by studying posturography in 46 patients (23 CIDP and 23 CMT1A), the reality of the classical clinical clue of worse balance in CIDP than in CMT1A, despite similar sensory-motor impairment. We noticed that the posturographic RQ revealed a distinction between the two groups, whereas the Mariette clinical score did not show any

significant differences. Postural oscillations measured by stabilometry appeared to be more accurate than the clinician's eye in assessing balance disorders and visual dependence.

RQ-area and RQ-velocity were higher in the CIDP than in the CMT1A group (Fig. 1). Without vision, a moderate effect size was observed favoring a more significant deterioration in CIDP compared to CMT1A for RQ-area and a large effect size for RQ-velocity. Even though the RQ was higher in the CIDP group, we noticed that all patients were able to maintain postural balance eyes open for one minute.

As demonstrated by the RQ, this worsening was greater for CIDP patients than for CMT1A patients, with respective median RQ values of 2.42 and 1.75. Comparison with the literature revealed RQ values around 1.2 for healthy control groups (for subjects with an average age of 61 years [21]). The RQ results for our groups are consistent with values reported in other articles in the literature, with RQ values of 2.3 for CIDP groups [21] and 1.4 for overall CMT groups [22].

4.2. Velocity of CoP

Without vision, CoP velocity increased in the CIDP group but not in CMT1A group (Fig. 2-A). However, with and without vision, no difference was observed between the two groups. The CoP velocity is known to be correlated with loss of plantar flexor muscle volume [23], or with an increase in the co-contraction strategy of agonist and antagonist muscles of the leg [24–27]. In our population, the MRC of lower limb muscles did not differ between groups (e.g. MRC tibial and sural score) and did not seem to explain the increase of velocity in the CIDP group compared to the CMT1A group. It better reflected the agonist/antagonist co-contraction, related to the disequilibrium, and sometimes observed by the clinician as postural oscillations.

4.3. Area and sways parameters

To maintain the postural balance, subjects have to integrate their peripheral proprioceptive afferences, i.e. to adapt their posture according to the disequilibrium. In neuropathies, the

Table 3 – Posturography findings in CIDP and CMT1A in eyes open and eyes closed conditions.

	CIDP			CMT1A			CIDP vs CMT1A			
	Eyes open (n = 23)		Eyes closed (n = 23)	Eyes open (n = 23)		Eyes closed (n = 23)	Eyes open		Eyes closed	
	Median [Q1-Q3]	Median [Q1-Q3]	P-value	Median [Q1-Q3]	Median [Q1-Q3]	P-value	Hedge's g	P-value	Hedge's g	
Center of pressure Area (mm ²)	642.0 [412.5-1068.0]	1082.0 [846.5-2453.0]	< 0.0001*	449.0 [361.5-727.5]	840.0 [537.5-1101.5]	0.0002*	0.4990	0.4997	0.0226*	0.7227
Anteroposterior (mm)	31.3 [24.0-39.8]	41.1 [32.2-58.9]	< 0.0001*	22.7 [18.6-33.6]	33.5 [28.7-37.9]	0.0001*	0.3809	0.3921	0.0911	0.6137
Mediolateral (mm)	26.3 [20.4-38.1]	41.4 [36.3-58.6]	< 0.0001*	27.1 [22.9-32.2]	36.5 [27.3-41.9]	0.0084*	0.9750	0.2041	0.0316*	0.7557
Velocity (mm/s)	121.0 [105.1-146.3]	142.9 [128.0-160.6]	< 0.0001*	134.3 [121.7-161.1]	136.6 [125.6-172.9]	0.1986	0.3845	-0.4130	0.9992	-0.0271

Median values with interquartile ranges (Q1-Q3) for continuous variables. *P-values < 0.05, evaluated by mixed-effects model and Tukey post-hoc test.

afferences are impaired and the velocity of CoP displacement reflects the severity of the proprioception loss. The area of the posturography is the result of mediolateral and anteroposterior sways and reflects the quality of efferences. Anteroposterior sways are mainly driven by ankle oscillations whereas mediolateral sways are driven by the hips [28]. Concerning the mechanisms involved in the postural balance, our study showed that area and postural sways were similar in the two groups in the open eyes condition.

In the eyes closed condition (Fig 2), all evaluated parameters (area, anteroposterior and mediolateral sways) deteriorated in both groups. The area differed between groups, related to the strong differences in mediolateral sway, which was greater in the CIDP group. The poor regulation of hip control mechanisms in the CIDP group in the eyes closed condition could be related to greater fear of falling in this group (to be further evaluated) or also to a more pronounced proximal sensory-motor deficiency in the CIDP group (known by clinicians even if no MRC differences between groups was observed in our study). The impact of fear of falling is well documented not only in the general population but also in populations with diabetic neuropathy [29-31]. Anteroposterior sways were the same in the two groups and a moderate Hedge's g effect size (g = 0.6137) was not enough to conclude that anteroposterior sways were more pronounced in the CIDP group. These results on sways and area parameters, along with the decrease in mediolateral sway, reflect a "block strategy" with fewer ankle and hip oscillations [25,26,32].

Our results suggest that the CMT1A patients experienced more severe secondary axonal loss compared to the CIDP patients (usually with no EDX responses in the lower limb or more pronounced responses than in the CIDP group for the median and fibular nerve) but with a postural control at least as good as the CIDP group in the open eyes condition. However, sensory functions, as assessed by physical examination and the INCAT score, showed no differences. Arthrokinesthesia and pallesthesia were similar between the two groups. This would likely be a development of compensatory mechanisms. It seems that the patients with CMT1A depended less on proprioceptive feedback to maintain their balance than the CIDP patients. Visuo-dependence was present in CMT1A patients, but visual deprivation destabilized them less compared to CIDP patients as observed with the RQ. There are likely compensatory mechanisms, such as the development of hyper-rigidity strategies in the trunk or other mechanisms resulting probably from the long duration of the disease and the patient's unconscious comprehension that for balance it is better to neglect these proprioceptive afferences. Further studies are needed and currently underway to deepen our understanding of the mechanisms involved. Another study on additional adaptation mechanisms will complement these initial findings and try to study the impact of vestibular afferences. It is known that some vestibulopathies also are possible in CMT1A patients and that the quality of these afferences is probably not better in CMT1A patients than in CIDP patients. The better postural response is probably much involved with postural fixation and we should further study the trunk.

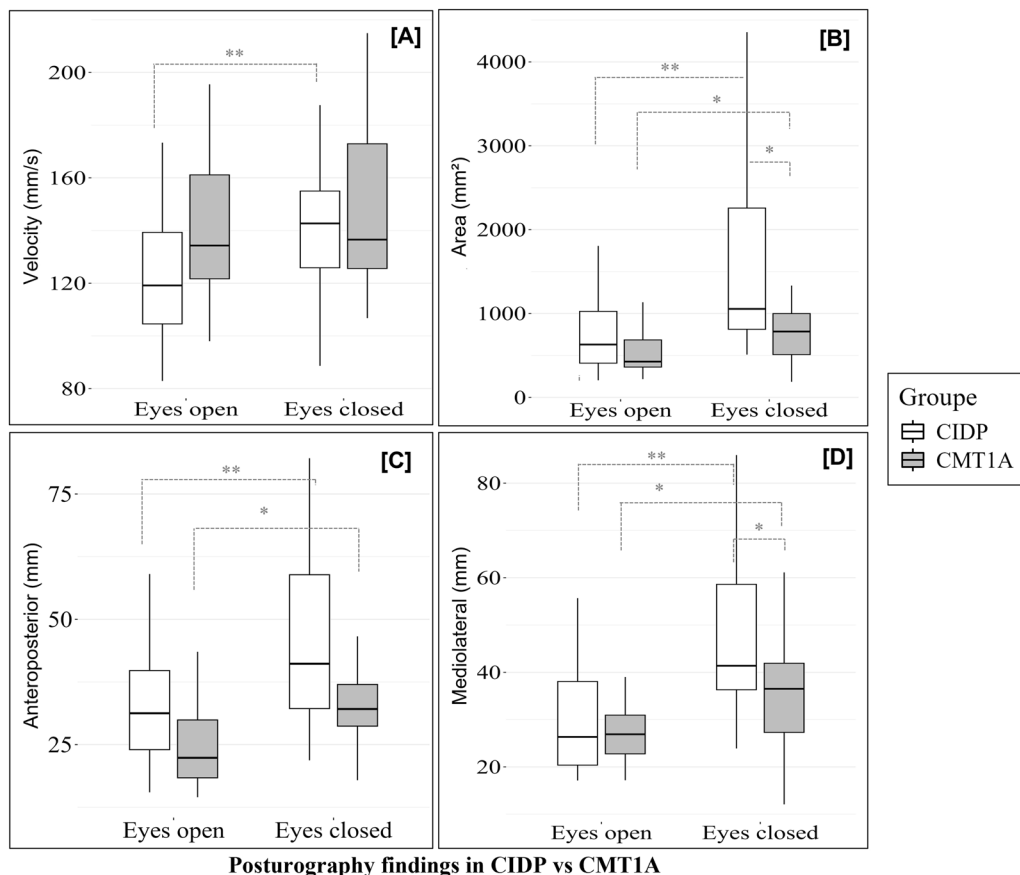


Fig. 2 – Descriptive plots of velocity [A], area [B], anteroposterior sway [C] and mediolateral sway [D] in open and closed eyes conditions. A. Velocity was increased in the CIDP group under eyes-closed condition compared to eyes-open condition, but does not differ for the CMT1A group and between two groups. B. Area was increased in both groups under eyes-closed condition compared to eyes-open condition. In the eyes-closed condition, the area was higher in CIDP patients than in CMT1A patients. C. Anteroposterior sways were increased in both groups under eyes-closed condition compared to eyes-open condition; under eyes-closed condition, there was no difference observed between the two groups. D. Mediolateral sways were increased in both groups under eyes-closed condition compared to eyes-open condition; under eyes-closed condition, mediolateral sway was greater in CIDP patients than in CMT1A patients. *P-values ≤ 0.05 , **P-values ≤ 0.0001 , evaluated by mixed-effects model and Tukey post-hoc test.

5. Limitations

The main limitation of this pilot study is the small sample size. CIDP and CMT1A are rare diseases, and recruitment from a single center did not allow for the recruitment of a large number of patients, although it had the advantage of harmonized records. Even though we observed group differences, our sample did not enable us to identify a cut-off to discriminate the two populations. Nevertheless, we observed that no CMT1A patient had a RQ > 3.5 (Fig. 1) and further studies could be proposed to validate the sensitivity and specificity of this cut-off as a diagnostic biomarker (to distinguish CIDP and CMT patients with complex clinical or EDX presentations). The issue that almost all CIDP patients were treated and stable on IVIg treatment should also be addressed; maybe RQ could also be evaluated according to disease course and treatment response. EDX examinations were not systematically

controlled in CMT1A patients, which does not allow for an optimal comparison of NCV data. Even though the posturographic evaluation was informative, in clinical practice, RQ-Area and RQ-Velocity are not readily available and require access to a technical facilities, which can be challenging in routine care.

6. Conclusion

In conclusion, this original study highlights the value of a quantitative and simple approach to assess postural balance in the evaluation and comparison of hereditary and acquired neuropathies. Furthermore, posturography parameters appear to be different between the two groups, whereas traditional clinical data showed no differences. More extensive investigations will be necessary to confirm these preliminary results and provide additional evidence.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.neurol.2024.10.002](https://doi.org/10.1016/j.neurol.2024.10.002).

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