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Article *in* Gait & posture · July 2016

DOI: 10.1016/j.gaitpost.2016.07.183

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Postural instability in Charcot-Marie-Tooth 1A disease

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ARTICLE INFO

Article history:
Received 2 October 2015
Received in revised form 22 July 2016
Accepted 26 July 2016

Keywords:
Charcot-Marie-Tooth
Postural imbalance
Distal muscle weakness

ABSTRACT

The aim of this study was to evaluate the influence of somatosensory impairment, distal muscle weakness and foot deformities on the balance in 21 CMT1A patients using a baropodometric platform.

Stabilometric analysis by measuring sway area and velocity of a centre of pressure (CoP) both at open and closed eyes were used to assess postural imbalance. Static analysis, by measuring the load and the plantar surface of forefoot, midfoot and hindfoot was used to define the footprint shape and to assess as a whole foot deformities. Stabilometric and static results were compared with those of a control group. In CMT1A patients, stabilometric findings were correlated with static parameters, Achilles' tendon retraction, distal muscle strength and CMT examination score (CMTES). CMT1A patients compared to controls had lower plantar surface and load on midfoot, and higher load on a forefoot. CMT1A patients had a greater postural instability, since they had a higher CoP velocity, both at open and closed eyes. Moreover, the CoP velocity correlated inversely with the strength of ankle dorsi-flexion muscles and directly with CMTES as whole and with the item "*motor symptoms legs*". Postural imbalance was not correlated with sensory impairment and foot deformities as expressed by static analysis and Achilles' tendon retraction.

In this study we demonstrated an altered balance in CMT1A patients during upright standing. The imbalance in our CMT patients seems to be related to the weakness of ankle dorsi-flexor muscles rather than sensory impairment or foot deformities. These results could be due to a mildly affected CMT1A population, evaluated in an early stage of the disease.

1. Introduction

Charcot-Marie-Tooth disease (CMT) is a hereditary motor sensory neuropathy. The most common subtype is CMT1A, a demyelinating form due to duplication in chromosome 17p11.2 [1]. The clinical features are progressive distal muscular atrophy and weakness, sensory loss, decrease or absence of deep tendon reflexes, and skeletal deformities (i.e. pes cavus, scoliosis etc.) [2]. Balance disturbances represent limiting factors for physical daily activity in CMT disease [3]. However, postural instability is still a critical aspect of CMT, since it has been scarcely investigated so far, and the basis of postural imbalance in CMT remains controversial.

In CMT1A patients, sensory deficit and distal muscle weakness have been invoked in pathogenesis of postural imbalance [4–8]. Nardone et al. [4] have not found a correlation between postural instability and sensory deficit whereas other authors have demonstrated the influence of proprioception [5] and pinprick [8] impairment on postural control in CMT1A patients. Moreover, some studies have focused their attention on ankle plantar-flexor muscle weakness as the main factor for postural instability [6,8].

Other factors that could influence postural stability in CMT disease are structural foot deformities [9,10] including foot bone deformities (e.g. pes cavus) as well as Achilles' tendon shortening. The influence of foot deformity on balance, to our knowledge, has never been systematically investigated in CMT disease. However, it is likely that foot bone deformities may influence postural balance, since the foot, during upright standing, must be able to adapt to the ground surface in order to optimize stability as needed [11,12]. Likewise, Achilles' tendon shortening, may alter the foot mobility and reduce the ability to function optimally during quiet standing.

The aim of the present study was to investigate, by using a baropodometric platform, the influence of somatosensory

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http://dx.doi.org/10.1016/j.gaitpost.2016.07.183
0966-6362/

impairment, distal muscle weakness and foot deformities on postural stability in a group of CMT1A patients.

2. Patients and methods

2.1. Subject and clinical evaluation

Twenty-one CMT1A patients (11 females; mean age 38.8 + 16.9 years) and 24 mean age-matched controls (13 females; mean age 43.0 + 20.8 years) were recruited for the study. Clinical data of patients are summarized in Table 1. Extended clinical data are reported in Supplementary Table 1. All subjects signed a written informed consent before enrolling into the study.

All CMT1A patients underwent standard neurological evaluation. Overall, clinical disability was assessed by applying CMT Examination Score (CMTES), a compound scale of disability (ranging from 0 no disability, to 28 maximum disability), calculated as the sum of the symptoms (sensory and motor) and the signs (pin sensibility, vibration, strength of legs and arms) [13]. The strength of ankle plantar-flexor and dorsi-flexor muscles was evaluated according to MRC scale (0 no movement, 5 normal strength).

For the retraction of Achilles' tendon (ankle Range of Motion ROM), patients were positioned seated and the ankle joint was moved passively to its full dorsi-flexion extent. The degree of angle between the long axis of the fibula and the head of the fifth metatarsal was measured using a goniometer.

2.2. Protocol procedure

All subjects underwent static and stabilometric analysis, using the freeMed ®120 × 50 cm baropodometric platform (produced by Sensor Medica, Guidonia Montecelio, Roma, Italy) in combination with FreeStep® software (http://www.sensormedica.com/site/en/software/software-for-biomechanic-analysis). During analysis patients and healthy controls were in standing position on a stable platform, barefoot and without ankle foot orthosis.

During the static analysis the subjects were standing for 5 s on the platform and software automatically identified three areas of foot (forefoot, midfoot and hindfoot) by dividing the length of the footprint into equal thirds, and calculated the load and the plantar surface for each of them.

The load on forefoot, midfoot and hindfoot was reported as percentage of total load of both feet.

The plantar surface of forefoot, midfoot and hindfoot was measured in cm^2; however, to reduce bias due to different foot size, we have normalized this measure by calculating for each foot the three percentages of plantar surface.

Data obtained from static analysis were used to define the footprint shape in patients and controls, and to assess as a whole foot deformities in CMT1A patients.

During stabilometric analysis the subjects were standing for 51 s on the platform, with feet spaced 10 cm and arms alongside trunk, firstly with open eyes (OE) and then with closed eyes (CE), in order to evaluate postural stability by recording sway area (mm^2) and mean velocity of Centre of Pressure (CoP; mm/s). The extent of worsening for each parameter during the visual deprivation was expressed by Romberg index, calculated as the ratio between the values at CE and OE conditions (CE/OE × 100) [14].

2.3. Statistical analysis

Parametric and non-parametric variables are reported as mean ± standard deviation (SD) or median value (25th–75th ‰), respectively. Accordingly, comparison among control subjects and patients was based on either the Student *t* Test for independent samples or the nonparametric Mann-Whitney *U* test. In CMT1A patients the Spearman coefficient was computed to investigate the correlations between the different variables. The statistical significance level was set at 5% (alpha = 0.05) and two-tailed tests were used throughout. Confidence intervals are based on 95% confidence level. All the statistical analyses have been realized using R version 3.2.

3. Results

Static and stabilometric results from patients and controls are summarized in Table 2.

Briefly, static analysis showed that CMT1A patients had a different footprint shape respect to control group. Notably, CMT1A patients showed smaller plantar surface and load on midfoot, and higher load on a forefoot. These findings were consistent with typical profile of pes cavus [15].

The stabilometric analysis demonstrated that CMT1A patients had a greater postural instability than controls since they had a higher mean velocity of CoP, both at open and closed eyes. The sway area was not different between patients and controls. Moreover, the sway area was not different between the upright standing at open eyes and closed eyes in both groups.

The Romberg index, expression of the extent of worsening of these parameters when recorded at open and closed eyes, was not different between patients and controls.

The CoP velocity, both at open and closed eyes, correlated inversely, with the strength of ankle dorsi-flexion muscles as assessed by MRC scale (OE, right side $rho = -0.5$, $p = 0.01$; OE, left side $rho = -0.4$; $p = 0.04$; CE, right side $rho = -0.5$, $p = 0.01$; OE, left side $rho = -0.4$; $p = 0.02$) and directly with CMTES as whole (OE, $rho = 0.4$, $p = 0.03$; CE, $rho = 0.5$, $p = 0.01$) and with the item "*motor symptoms legs*" (OE, $rho = 0.6$; $p = 0.001$; CE, $rho = 0.5$; $p = 0.01$) (Fig. 1). No correlation was found between the CoP velocity with age of patients, other CMTES items and strength of ankle plantar-flexion muscles.

Lastly, no correlation was found between stabilometric data and foot deformities as evaluated by static analysis (i.e. load and plantar surface of forefoot, midfoot and hindfoot) and ankle range of motion (ROM).

4. Discussion

In this study, we demonstrated that CMT1A patients with mild disability were less stable than controls during upright standing. Technically, the velocity of CoP rather than the sway area was the

Table 1
Clinical data of CMT1A patients.

	CMT1A	Range
CMTES	4 [2; 8] (0–16)	(0–28)
Sensory symptoms	0 [0; 0] (0–2)	(0–4)
Motor symptoms legs	1 [0; 1] (0–2)	(0–4)
Motor symptoms arms	1 [0; 1] (0–2)	(0–4)
Pinprick	1 [0; 1] (0–2)	(0–4)
Vibration	1 [1; 2] (0–3)	(0–4)
Strength legs	1 [0; 1] (0–4)	(0–4)
Strength arms	0 [0; 1] (0–2)	(0–4)
MRC ADF dominant	4 [4; 5] (0–5)	(0–5)
MRC ADF non-dominant	4 [4; 5] (0–5)	(0–5)
MRC APF dominant	5 [5; 5] (1–5)	(0–5)
MRC APF non-dominant	5 [5; 5] (1–5)	(0–5)
Passive ankle ROM dominant (degree)	35 [22; 40] (50–100)	NA
Passive ankle ROM non-dominant (degree)	35 [22; 40] (50–100)	NA

Data are expressed as median [25th; 75th ‰] and range is reported in brackets; CMTES, Charcot-Marie-Tooth Examination Score; MRC, Medical Research Council scale for muscle strength; ADF, Ankle Dorsi-Flexor; APF, Ankle Plantar-Flexor; ROM, Range of Motion.

Table 2
Static and stabilometric data of CMT1A patients and controls.

	CMT1A	Controls	p-value
Static analysis			
Load forefoot L (%)	27 [22.5; 31]	20 [15; 24]	<**0.001**
Load forefoot R (%)	25 [22.5; 30.5]	19.5 [14.2; 24.7]	**0.001**
Load forefoot (L and R)	27 [23; 29.5]	20 [16.5; 22.2]	**0.0001**
Load midfoot L (%)	4 [1.5; 6]	7 [4.5; 9.7]	**0.011**
Load midfoot R (%)	3 [0.5; 5.5]	7 [4; 10]	**0.003**
Load midfoot (L and R)	3.5 [2; 6]	7.7 [4.7; 10]	**0.0037**
Load hindfoot L (%)	20 [18; 24]	22.5 [18.5; 24]	0.164
Load hindfoot R (%)	17 [13.5; 20]	23 [18.2; 24]	**0.008**
Load hindfoot (L and R)	18.5 [16; 21.5]	23 [18.7; 24.2]	**0.0208**
Plantar surface forefoot L (%)	50 [42.5; 54]	45 [42; 51.7]	0.473
Plantar surface forefoot R (%)	49 [44; 56]	47 [39.2; 53]	0.175
Plantar surface forefoot (L and R)	50.5 [45.5; 55]	47.5 [40; 50.5]	0.2319
Plantar surface midfoot L (%)	10 [5.5; 22]	23 [17.5; 25.7]	**0.003**
Plantar surface midfoot R (%)	9 [2.5; 17.5]	20 [16.2; 27.5]	<**0.001**
Plantar surface midfoot (L and R)	10.5 [5; 16.5]	21.7 [18.2; 26.7]	**0.0003**
Plantar surface hindfoot L (%)	32 [28; 35.5]	32 [28.2; 35.5]	0.977
Plantar surface hindfoot R (%)	29 [26; 32]	31 [27.2; 34.7]	0.132
Plantar surface hindfoot (L and R)	30.5 [27; 33.5]	32.2 [28.7; 34.2]	0.4591
Stabilometric analysis			
Sway area OE (mm^2)	92.3 [48.6; 266.3]	84 [46; 124.5]	0.612
Sway area CE (mm^2)	83.8 [34.7; 594.8]	65.5 [36.7; 81]	0.215
Velocity of Cop OE (mm/s)	21.43 [15.7; 32]	15 [12; 18]	**0.001**
Velocity of CoP CE (mm/s)	30.2 [18.5; 42.7]	16 [12.5; 19]	<**0.001**
RI sway area (CE/OE)	107 [47; 305]	89 [32.2; 147]	0.28
RI velocity of CoP (CE/OE)	109 [101.5; 131.5]	106.5 [102; 116.7]	0.446

Data are expressed as median [25th; 75th ‰]; statistically significant differences are printed in bold; R, right; L, left; OE, open eyes; CE, closed eyes; CoP, centre of pressure; RI, Romberg Index.

stabilometric parameters that reflected postural imbalance in our population. Our findings, regarding stabilometric analysis, are in line with previous reports that demonstrated that the velocity of CoP is more sensitive than sway area in depict quiet stance impairment [4,5]. Moreover, we found that postural instability correlated with ankle dorsi-flexor muscle weakness, with a higher grade of disability as expressed by CMTES as whole and only with the CMTES item "*motor symptoms legs*".

We cannot exclude that the narrow scatter of data for each CMTES item may have prevented to find other correlations.

Anyway, the correlation between CoP velocity and weakness of dorsi-flexor muscles raises some points of discussion. Actually, it can be difficult to understand why there is an association between postural imbalance and ankle dorsi-flexor muscle weakness since these are not antigravity muscles. Although posterior muscles of leg play certainly a major role in quiet standing [16], also anterior muscles of leg activate during upright stance and this co-activation has a stabilizing effect on postural sway [17,18]. It is conceivable that under conditions of increased muscle weakness this co-activation is altered, resulting in deterioration of postural control. Therefore, we believe that the weakness of dorsiflexor muscles can have influenced postural balance in our CMT1A patients. However, other authors underlined that in CMT1A patients the plantar-flexor muscles are detrimental to the postural control during upright stance [6,8]. The natural history of CMT1A might easily explain this difference. The plantar-flexor muscle weakness usually occurs later in the CMT disease course [19] and is associated to a more severe clinical impairment and a greater deterioration in postural control [20]. Given this, our patients were younger and less severely affected (lower CMTES) than those previously described [6,8]. Noteworthy, almost all of our patients were able to walk on tiptoes, suggesting a relative sparing of posterior leg muscles.

Sensory deficits, including proprioception [5] and pinprick [8], have been also involved as possible cause of the postural instability in CMT1A.

Actually, a single report pointed out the proprioception as cause of postural instability [5] while other studies have not confirmed this finding [4,7,8]. We have not found any correlation with the item "*vibration*" of CMTES and, interestingly, postural stability at closed eyes worsened to the same extent in patients and controls. These data suggest that, during visual deprivation, proprioception impairment is not a major factor in postural instability in our CMT1A population that is mildly affected.

Moreover, we have not observed any correlation between pinprick deficits and postural instability as instead recently described by some authors [8]. A higher damage of pinprick (range 0–4) reported by Lencioni et al. [8] compared to our results (range 0–2) could account for this discrepancy.

However, these authors have found this correlation only when evaluating a group of CMT patients including different genotypes (CMT1A, CMTX and CMT2) [7,8]. Hence, the potential role of pinprick in postural instability in CMT1A remains still to be defined.

In addition, foot deformities might play a further role in postural instability in CMT1A patients. As expected, we found a different footprint shape in CMT1A patients compared to controls. However, we did not find in our CMT1A patients any correlation between postural balance and footprint features. Similarly, no correlation was found between ankle ROM and postural stability. Overall, foot deformities appear in early stages of disease [21], and it is likely that, in adulthood, compensatory mechanisms on postural balance have been already occurred making the effect of foot or ankle structural changes less relevant.

In conclusion, our findings support the role of distal muscle weakness at lower limbs in determining postural instability in

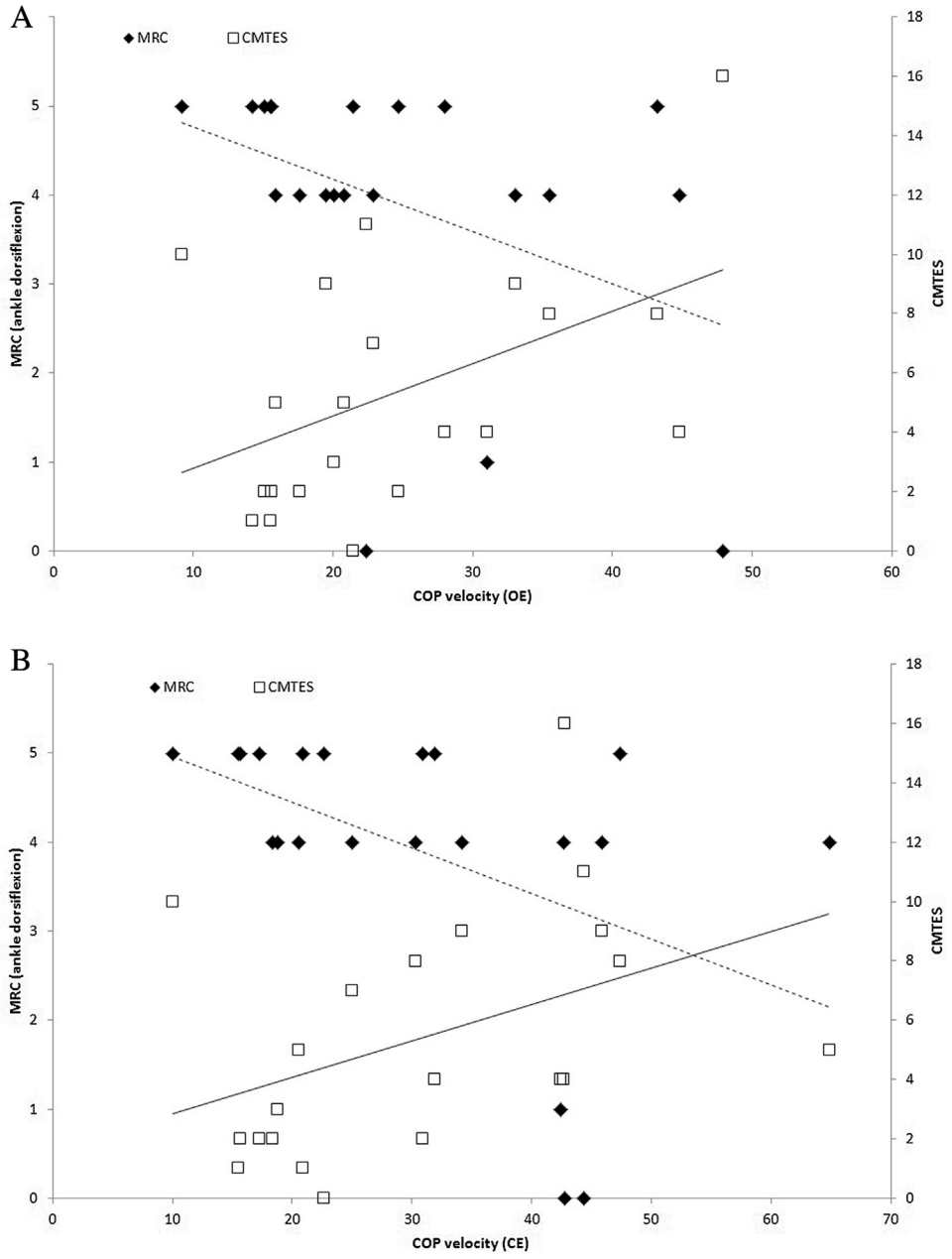

Fig. 1. Scatterplot of Centre of Pressure (CoP) velocity at open (A) and closed (B) eyes *vs* MRC of ankle dorsiflexion (dotted line) and CMTES (continuous line).

CMT1A rather than sensory deficits and foot deformities. Rehabilitation programs, aimed to improve postural balance in CMT1A patients, should take into account proper exercises to maintain distal muscle strength.

Acknowledgement

No acknowledgement.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.gaitpost.2016.07.183.

Conflict of interest

None of the authors had any financial or personal relationships with other people or organizations that could inappropriately influence their work.

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