Research in Developmental Disabilities 34 (2013) 840–846

Contents lists available at SciVerse ScienceDirect

Research in Developmental Disabilities

Measuring regularity of human postural sway using approximate entropy and sample entropy in patients with Ehlers–Danlos syndrome hypermobility type

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ARTICLE INFO

Article history:
Received 12 September 2012
Received in revised form 9 November 2012
Accepted 9 November 2012
Available online 12 December 2012

Keywords:
Ehlers–Danlos syndrome
Postural analysis
Entropy analysis

ABSTRACT

Ligament laxity in Ehlers–Danlos syndrome hypermobility type (EDS-HT) patients can influence the intrinsic information about posture and movement and can have a negative effect on the appropriateness of postural reactions. Several measures have been proposed in literature to describe the planar migration of CoP over the base of support, and the most used in clinical field are the CoP excursions in antero-posterior and medio-lateral direction. In recent years a growing number of studies have been designed to explore the complexity of the COP trajectories during quiet standing. We assessed 13 adults with EDS-HT (EDSG) and 20 healthy adults (CG) during static posture, evaluating the CoP using time and frequency domain analysis and entropy analysis (SampEn and ApEn parameters). Higher values of CoP displacements in medio-lateral and anterior–posterior directions for EDSG than CG were found; no differences were observed in CoP frequency. The entropy analysis showed lower value for EDSG than CG, pointing out the needing of EDSG to concentrate more attention on postural control, loosing complexity and reflecting a less automatized postural control.

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1. Introduction

Joint hypermobility syndrome (JHS) is a relatively common, although largely under diagnosed clinical entity, characterized by congenital contortionism and additional musculoskeletal complaints (Steinmann, Royce, & Superti-Furga, 2002). There is a significant clinical overlap with various heritable connective tissue disorders, mainly the Ehlers–Danlos syndrome(s) (EDS) (Grahame, Bird, & Child, 2000). These similarities are so stringent that, recently, an international group of experts stated that JHS and EDS hypermobility type (EDS-HT) are the same clinical entity that should be distinguished from other types of EDS (Tinkle et al., 2009). Major features include joint hypermobility, joint complications and minor skin features (e.g., skin hyperextensibility), while the presence of additional cutaneous, vascular, skeletal and ocular findings moves towards the diagnosis of other EDS variants. Hypotonia in EDS-HT patients can influence the intrinsic information about posture and movement and can have a negative effect on the appropriateness of co-contraction and postural reactions. Increased joint mobility may contribute in a negative sense to postural control: hypermobility may affect the stability based on faulty reflex pattern originating from tendon organs (Røgind, Lykkegaard, Bliddal, & Danneskiold-Samsøe, 2003). Together with

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0891-4222/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ridd.2012.11.007

insufficiency of co-contraction this will influence the stability of joint. Their impaired postural control (Galli, Cimolin, et al., 2011; Galli, Rigoldi, et al., 2011; Stanitski, Nadjarian, Stanitski, Bawle, & Tsipouras, 2000) tends to progressively worsen as the clinical picture advances, severely limiting the patients' quality of life; as balance represents a key function for performing daily life tasks, its quantification represents a milestone for planning appropriate rehabilitation interventions.

Among the several experimental techniques available to investigate postural control in quiet standing, platform posturography is the most widely used: force platforms measure the fluctuations of the centre of pressure (CoP), which represents the point of contact under the feet through which the ground reaction forces are considered to act. In particular, static posturography is very easily to be acquired in everyday practice, especially in pathological conditions, for the simplicity of the experimental set-up and its safety. Several measures have been proposed in literature to describe the planar migration of CoP over the base of support, and the most used in clinical field are the CoP excursions in antero-posterior and medio-lateral direction.

In recent years a growing number of studies have been designed to explore the complexity of the COP trajectories during quiet standing. Given that during quiet stance the displacements of the COP display highly irregular and non-stationary fluctuations, the analysis of COP dynamics could contain and consequently add information about the postural control exerted. The quantification of the complexity or chaos, in terms of irregularity, could be measured using entropy, defined as a quantity measuring the rate of generation of information (Roerdink et al., 2011a; Roerdink, Hlavackova, & Vuillerme, 2011a, 2011b). In literature, several algorithms were proposed for estimating entropy of a system from a time series. In particular, Pincus (1991) developed a family of statistics, namely the approximate entropy (ApEn index), which has the advantage to be apply both to deterministic and stochastic systems, so in a variety of contexts. This feature makes this parameter one of the most popular metrics used to estimate complexity and regularity in the field of biomedical signal analysis (Aboy, Cuesta-Frau, Austin, & Mico-Tormos, 2007; Pincus & Singer, 1998). However, this method has some biases: firstly it is dependent on the record length and it is lower than expected for short records; then it lacks relative consistency (Richman & Moorman, 2000). To solve these problems, more recently, Richman and Moorman (2000) modified the ApEn method and developed a new parameter, the sample entropy (SampEn index). The SampEn parameter is independent of the record length, is characterized by relative consistency and its algorithm is simpler than the ApEn, needing lower time for computation (Ramdani, Seigle, Lagarde, Bouchara, & Bernard, 2009).

In recent literature, several studies have been addressed to characterize the effects of a broad set of functionally relevant factors on postural stability: these proposals were based on the empirical findings that COP trajectories were more regular (low value of measured entropy) for pathological groups than for controls and on the assumption that COP fluctuations provide a complex output signal of the postural control system in which various pertinent cognitive, perceptual and motor processes are reflected. Roerdink et al. (2006) proposed a direct relation between the amount of attention used in maintaining postural control and the regularity of COP signal: according to their findings, COP trajectories were more regular in stroke patients than in controls and became less regular when performing a secondary cognitive task while standing, reflecting that the measure of the complexity or irregularity of a system is linked to the concept of efficiency or automaticity of postural control. More regular posturograms are associated with increased attentional investments in postural control, in other words, more regular COP signals reflect less automaticity. A decrease in complexity of a physiological time series is indicative of a decrease in healthiness of effectiveness of the physiological control system (Donker, Roerdink, Greven, & Beek, 2007; Goldberger et al., 2002): increased COP regularity may be explained as an indication of an increasingly ineffective postural control strategies.

Starting from these assumptions, several authors reported that through the computation of entropy has been possible to assess specific postural behaviours induced by age, health status, postural task and cognitive contexts (Donker et al., 2007; Ramdani et al., 2009; Roerdink et al., 2006; Stins, Michielsen, Roerdink, & Beek, 2009). In particular, in a more recent study, Roerdink et al. (2011a, 2011b) reported the effects of plantar flexor muscle fatigue on the regularity of COP signal: their finding was that anterior–posterior COP fluctuations were more regular with than without fatigued of plantar-flexor muscles. According to the previously proposed relation between COP regularity and the amount of attention, the authors suggested that standing quietly upright with fatigued plantar flexors may be manifested by a deliberate increase in sway magnitude to indirectly evocate and to exploit the vestibular system, which is accompanied by an increased attentional investment to closely monitor and control posture.

According to these findings and given that the EDS-HT patients are characterized by an increased joint mobility that may contribute in a negative sense to postural control in terms of proprioceptive feedback, in this study we expect to observe larger COP fluctuations for EDS-HT patients than for controls, quantified by the conventional posturographic measures both in time and frequency domain, and to observe a loss of complexity (and consequently automaticity) in the postural control reflecting an increased ineffective postural control strategies with attentional investments in evoking vestibular control, quantified by the measure of approximate and sample entropy.

2. Materials and methods

2.1. Participants

We enrolled 20 individuals as controls (control group: CG) and 13 EDS-HT adult patients matched for age. Exclusion criteria for the CG included prior history of cardiovascular, neurological or musculoskeletal disorders. They showed negative

Beighton score, normal flexibility and muscle strength and no obvious gait abnormalities. They were recruited among university students and workers. EDS-HT patients were all referred to the "Joint hypermobility service" of Physical Medicine and Rehabilitation Division of Umberto I Hospital in Rome undergoing multidisciplinary rehabilitation in different settings (out-patient); they were evaluated in the motion analysis lab of IRCCS San Raffaele-Pisana in Rome. The diagnosis of EDS-HT was established using published criteria (Beighton, De Paepe, Steinmann, Tsipouras, & Wenstrup, 1997; Grahame et al., 2000) and participants were considered affected if meeting at least one of the two sets of diagnostic criteria. Additional extra-articular features were also investigated and registered accordingly. As joint hypermobility syndrome/Ehlers–Danlos syndrome (JHS/EDS-HT) is a diagnosis of exclusion, the absence of features suggestive of other heritable connective tissue disorders was assessed in a clinical genetics outpatient facility EDS-HT patients were able to understand and complete the test.

All participants were free from conditions associated with impaired balance, vision loss/alteration, vestibular impairments, neuropathy, as detected by the clinical examination, intracranial hypertension.

In Table 1 the characteristics of CG and EDSG are reported.

The study was approved by the Ethics Committees of the Institute. Written informed consent was obtained by the patients.

2.2. Stabilometric test

Postural sway was measured for 30 s while participants stood on a force platform (Kistler, CH; acquisition frequency: 500 Hz) with a fixed position of feet (30° with respect to the AP direction) integrated with a video system (BTS, It). They were asked to keep their arms held alongside and to focus on a visual reference mark fixed 1.5 m in front of them at the individual line of vision. Two experimental session conditions were tested: with eyes-open (EO) and eyes-closed (EC). To avoid any kind of learning or fatigue effect (Tarantola, Nardone, Tacchini, & Schieppati, 1997) one trial was acquired with OE and one with CE and between each trial participants were allowed to rest and sit down for 2 min, still maintaining the feet position throughout the trials. The used experimental set-up was according to previous studies (Cimolin, Galli, Vismara, et al., 2011; Cimolin, Galli, Rigoldi, et al., 2011; Galli, Cimolin, et al., 2011; Galli, Rigoldi, et al., 2011).

The same experimenter verbally requested the test without providing any modelling or prompting instructions. If the subject was not able to execute the action on verbal request, additional help was given in the following order: (1) verbal prompting: cues and hints; (2) modelling prompt: action first demonstrated by the operator (i.e. "Watch me, look in front of you the black target, please maintain the arm at your side, . . .").

2.3. Postural parameters

The outputs of the force platform allowed us to compute the CoP time series in the A/P direction (CoPAP) and the M/L direction (CoPML). The first 10 s interval was discarded in order to avoid the transition phase in reaching the postural steady state (Galli et al., 2008). The output of the platform was processed to compute quantitative parameters in time and frequency-domain, demonstrated to be significant for the postural analysis in EDS-HT patients (Galli, Cimolin, et al., 2011; Galli, Rigoldi, et al., 2011), as well as using entropy algorithms. In particular the following parameters were considered.

2.3.1. Time-domain parameters

The antero-posterior and medio-lateral coordinates of the CoP trajectory underwent a post-acquisition filtering using a low-pass filter with a cut-off frequency of 10 Hz (Schmid, Conforto, Camomilla, Cappozzo, & D'Alessio, 2002). As for time-domain analysis, the following parameters were identified and computed:

- RANGE: the range of CoP displacement in the A/P direction (RANGEAP index) and the M/L direction (RANGEML index), expressed in mm.
- Trajectory length (TL): the total CoP trajectory length, expressed in mm.

All parameters were normalized to the participant's height (expressed in metres), according to literature (Rocchi, Chiari, & Cappello, 2004), in order to avoid the influence of different subject's height on the results.

Table 1
Clinical characteristics of the study groups (EDSG, Ehlers–Danlos syndrome group; CG, control group). Data are expressed as mean (standard deviation).

	EDSG	CG
Participants	13	20
Age (years)	32.4 (8.4)	31.4 (9.6)
Height (cm)	163.1 (9.0)*	173.3 (5.1)
Weight (kg)	65.4 (17.1)	62.6 (8.5)

* $p < 0.05$, EDSG vs. CG.

2.3.2. Frequency domain parameters

The commonly used method to describe posture in the frequency domain is the non-parametric method, which utilizes the fast Fourier transform. When dealing with pseudo-stochastic signals, the use of parametric power spectrum estimators, such as those based on AutoRegressive models of the data which we used in our analysis, may have some advantages, especially when short data segments are available and few harmonic components have to be retrieved from a wide-band noise (Mendez Garcia & Mainardi, 2006).

With regard to the frequency analysis of the postural sway, the signals were firstly down-sampled (anti-aliasing filter) at 10 Hz. The analysis was performed using parametric estimators based on autoregressive (AR) modelling of the data (Galli et al., 2008).

In this study we considered the following frequency-domain parameters:

- the centre frequency of the spectral power peak of the Py spectrum (fy);
- the centre frequency of the spectral power peak of the Px spectrum (fx).

2.3.3. Entropy algorithms

Let $x(t)$ be the temporal evolution of a given signal and S its discrete-time version, obtained by a regular sampling. We have (1)

$$S = \{x_k, k = 1, \ldots, K\} \tag{1}$$

where x_k stands for $x(t_k)$, i.e., the signal value at the time $t_k = k^*T$, T is the sampling period and K is the number of samples. Let us define the pattern $p_m(i) = \{x_i, x_{i+1}, \ldots x_{i+m-1}\}$ as the sequence of m samples beginning with x_i, Two patterns, $p_m(i)$ and $p_m(j)$, are considered similar if the difference between any pair of corresponding measurements in the patterns is less than the tolerance r, i.e., if (2)

$$|x_{i+k} - x_{j+k}| \quad \text{for} \ \ 0 \le k \le m \tag{2}$$

Considering the set P_m of all patterns of length m within S, we compute (3)

$$C_{im}(r) = \frac{n_{im}(r)}{N - m + 1} \tag{3}$$

where $n_{im}(r)$ is the number of patterns in P_m that are similar to $p_m(i)$. The quantity $C_{im}(r)$ is the fraction of patterns of length m that resemble the pattern of the same length that begins at sample i. $C_{im}(r)$ is calculated for each pattern in P_m and $C_m(r)$ is defined as the mean of the $C_{im}(r)$ values. The quantity $C_m(r)$ expresses the prevalence of repetitive patterns of length m in S. Finally, the ApEn of S, for patterns of length m and threshold r, is defined as (4)

$$ApEn(S, m, r) = \ln \frac{C_m(r)}{C_{m+1}(r)} \tag{4}$$

i.e., as the natural logarithm of the relative prevalence of repetitive patterns of length m compared with those of length $m + 1$.

The sample entropy (SampEn) is a modification of ApEn algorithm (Richman & Moorman, 2000) which has been shown to have lower bias. The differences are: (i) in the computation of $C_{im}(r)$, the cases in which $j = i$ are excluded to avoid counting the so-called “self matches”; (ii) in the computation of $C_m(r)$ and $C_{m+1}(r)$ the same number of templates $(N - m)$ are considered.

Both the indexes represent the complexity of the signal that has an inverse relationship with the repeatability of short sequences in the signal.

2.4. Statistical analysis

All the previously defined parameters were computed for each participant and then the median and interquartile range of all indexes were calculated for EDSG and CG. The Mann–Whitney *U*-test was used for comparing the normal controls and pathological participants. Then, in each group the EO and EC conditions were compared using Wilcoxon test in order to detect significant differences. With the proposed sample sizes the study will have a power of 80%. A statistically significant difference was accepted as $p < 0.05$.

3. Results

All the participants were able to perform the task without any difficulties and no interruptions occurred during test execution.

Age was not significantly different among groups. Weight was similar but EDS-HT participants' height was significantly different from CG: for this reason, in order to avoid the bias introduced by this difference, the reported values were normalized for individual height (expressed in metres).

Table 2
Postural parameters of the study groups (EDSG, Ehlers–Danlos syndrome group; CG, control group). Data are expressed as median (interquartile range). The values of the time domain parameters are normalized for the subject's height.

	EDSG		CG	
	Eyes-open	Eyes-closed	Eyes-open	Eyes-closed
Time domain				
RANGEAP (mm/m)	19.74 (7.98)$^{*,+}$	29.21 (15.52)*	6.23 (3.67)	6.51 (2.56)
RANGEML (mm/m)	13.51 (6.78)$^{*,+}$	21.89 (17.35)*	6.85 (3.19)	9.29 (3.98)
TL (mm/m)	892.56 (151.27)	936.89 (182.78)	704.73 (420.26)	759.76(106.92)
Frequency domain				
fx (Hz)	0.18 (0.17)	0.28 (0.19)	0.16 (0.18)	0.18 (0.13)
fy (Hz)	0.15 (0.19)	0.17 (0.18)	0.16 (0.21)	0.17 (0.19)
Entropy				
ApEn AP	0.06 (0.12)*	0.05 (0.10)*	0.24 (0.27)	0.34 (0.27)
ApEn ML	0.14 (0.17)*	0.15 (0.21)*	0.38 (0.31)	0.39 (0.28)
SampEn AP	0.05 (0.10)*	0.05 (0.08)*	0.18 (0.20)	0.24 (0.27)
SampEn ML	0.13 (0.16)*	0.13 (0.19)*	0.29 (0.21)	0.39 (0.22)

* $p < 0.05$, EDSG vs. CG.
$^{+}$ $p < 0.05$, EO vs. EC.

Table 2 displayed the mean and standard deviation of the computed parameters in time domain analysis of the COP signal.

The results of the analysis of the CoP in time domain are in line with previous findings (Galli, Cimolin, et al., 2011; Galli, Rigoldi, et al., 2011). In both OE and CE conditions, EDS-HT patients were characterized by greater displacements along both the antero-posterior and medio-lateral direction (RANGE AP and RANGE ML parameters) than controls. TL did not point out differences if compared to CG. No differences were found in control group between EO and EC conditions (Galli et al., 2008), while EDSG evidenced higher values of time domain parameters in EC condition than in EO condition.

Concerning the analysis of COP signal in frequency domain, our data showed that no significant differences emerged in the comparison between EDSG and CG, in both antero-posterior (Px parameter) and medio-lateral (Py parameter) directions, and in both conditions (EO vs. EC condition) evidencing that EDSG and CG are characterized by the same frequency in posture maintenance. These results are in line with previous study (Galli, Cimolin, et al., 2011; Galli, Rigoldi, et al., 2011).

Entropy parameters evidenced that EDS-HT participants were characterized by lower values in comparison with CG, with no differences between EO and EC, representing a loss of complexity in both conditions: the COP signal was more regular for pathological participants than for controls reflecting increasingly ineffective postural control strategies, as mentioned before.

4. Discussion and conclusion

The computed time domain parameters evidenced in our study more pronounced fluctuations in both directions for pathological participants than for controls: as expected, EDS-HT participants increased the range of motion of the COP, reflecting a less stable postural control. Our findings in this sense corroborated the results of previous study (Galli, Cimolin, et al., 2011; Galli, Rigoldi, et al., 2011), evidencing difficulties in controlling CoP displacements, trying to keep it inside the base of support using the plantar-flexor muscles (ankle strategy) alone, and pointing out that EDS-HT patients must rely also on hip strategy, as showed by the increased range of motion in ML direction (load–unload mechanism) in order to avoid the risk of fall. The comparison between time domain indexes in OE and CE condition revealed higher values of COP fluctuations in both direction for EDS-HT participants, reflecting that the closure of the eyes, and consequently the exclusion of visual feedback input, let the postural control be less stable.

Frequency analysis showed that EDS-HT patients displayed the same frequency of controls, even if the range of motion is higher in all directions. Since frequency parameters are related to the velocity at which the CoP moves, these results could underline that the changes in time domain did truly reflect the impairment in postural control, rather than a different strategy adopted by EDSG.

Considering the results of entropy analysis, EDS-HT patients evidenced lower value of both ApEn and SampEn in comparison with controls in both conditions. According to the past literature presented before, the decrease of the entropy is associated with a loss of complexity and a more regular COP signal. Maintaining and controlling quite stance requires a certain amount of attention (Donker et al., 2007; Woollacott & Shumway-Cook, 2002) even more in cases of the processing of information from somatosensory, visual and vestibular systems is reduced or a conflicting sensory information is present. EDS-HT patients are featured by a pronounced ligament laxity that, consequently with the presence of hypotonia, act in negative sense on somatosensory postural control feedback, increasing the attentional demands of visual and vestibular feedback systems: this is translated in less automaticity of the postural system, evidenced by a lower value of entropy.

Moreover, it has been postulated that the postural control system can adaptively reweigh the relative contribution of particular posture-specific sensory modalities, depending on the availability and reliability of the various sensory inputs in a given environmental context (Horak & Macpherson, 1996). In our study the alterated somatosensory feedback input, due to the alterated length of the tendons, probably evoked a higher demands for visual and vestibular feedback input. The alterations of somatosensory information in EDS-HT patients resulted in an overall increased magnitude of COP range of motion: typically, this increased postural sway is taken to reflect a degraded postural control. Given that an altered neuromuscular state is known to evoke centrally mediated adaptive changes of anticipatory postural adjustments (Strang & Berg, 2007; Strang, Berg, & Hieronymus, 2009; Strang, Choi, & Berg, 2008), and according to studies by Roerdink et al. (2011a, 2011b) and Strang, Haworth, Hieronymus, Walsh, and Smart (2011), this kind of patients probably adaptively compensated for the alteration of important posture-specific sensory inputs by deliberately increasing the magnitude of sway in order to get the vestibular system up and running (Roerdink et al., 2011a, 2011b). This adaptation is likely not an automatized postural response (Roerdink et al., 2011a, 2011b) and the decrease of entropy could reflect this less automatized postural control, indicative of an increased attentional investment according to the proposed relation between COP regularity and attentional investment in posture (Donker et al., 2007; Donker, Ledebt, Roerdink, Savelsbergh, & Beek, 2008; Roerdink et al., 2006, 2011a, 2011b; Stins et al., 2009). Conversely, the recorded differences between OE and CE condition in terms of COP range of motion is not observed for entropy parameters, even if, according to the relation between COP regularity and attentional investment in posture and excluding also the visual feedback inputs, the observed differences in time domain parameters made us hypothesized a more regular COP signal in CE condition than OE condition, as a reflection of a higher demand for vestibular response alone.

This study showed that the computation of entropy parameters adds information to the traditional time and frequency domain analysis of the CoP in individuals with EDS-HT, providing a more informative description of their dynamic posture, localizing the impairments that act on the postural system of people with EDS-HT.

The main limit of this study is the small number of enrolled participants which results in limited strength of the clinical and statistical findings. However, our investigation represents a preliminary attempt to integrate traditional posturographic methods with entropy computation of CoP during quiet stance in a pathological condition characterized by reduced balance capacity in order to evaluate the initial condition of the patient and in order to verify the outcomes of any applied treatments.

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