AUGMENTED MOVEMENT STRATEGIES FOR POSTURAL CONTROL IN PATIENTS WITH SPINOCEREBELLAR ATAXIA TYPE 3: A CASE-CONTROL STUDY

ESTRATÉGIAS AUMENTADAS DE MOVIMENTO PARA CONTROLE POSTURAL EM PACIENTES COM ATAXIA ESPINOCEREBELLAR TIPO 3: CASO-CONTROLE

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ABSTRACT
Introduction: This study investigated the movement strategies for postural control in patients with spinocerebellar ataxia type 3 (SCA3).

Methods: This case-control study enrolled 5 patients with SCA3 (aged 41 to 51 years) and 5 healthy participants group-matched by age, body mass and body height. Participants performed 3 trials lasting 30 s each of postural tasks characterized by: feet apart or together; eyes open or closed. Center of pressure (CoP) data was quantified using three-dimensional (3D: number of high-density and high-speed regions, average and maximal distances among regions), two-dimensional (2D: elliptical area, average velocity) and one-dimensional (1D: standard deviation, velocity) parameters.

Results: Analysis of variance revealed significant interaction effect between group*task for 1D (F₁₂,2₃₈=3.496, p<0.001), 2D (F₆,₃₈₄=11.472, p=0.004), and 3D parameters (F₁₂,2₃₈=2.54₃, p=0.004). Significant univariate effects for postural task were observed for all parameters, with higher body sway values under visual and biomechanical constraints, either separated or combined.

Conclusions: Patients with SCA3 presented augmented movement strategies compared with healthy subjects, characterized by increasing body sway under more demanding biomechanical and/or visual constraints. Three-dimensional kinematic mapping revealed either random movement strategies or a unique movement strategy characterized by a stochastic CoP distribution, with high CoP speed to correct for large body sway deviations.

Keywords: Machado-Joseph disease; Striatonigral Degeneration; Rehabilitation.

RESUMO
Introdução: Este estudo investigou as estratégias de movimento para controle postural em pacientes com ataxia espinocerebelar tipo 3 (SCA3). Métodos: Este estudo de caso-controle incluiu cinco pacientes com SCA3 (idade 41 a 51 anos) e cinco participantes saudáveis, agrupados por idade, massa corporal e altura corporal. Os participantes realizaram três ensaios 30 s cada uma das tarefas posturais caracterizadas por: pés separados ou juntos; olhos abertos ou fechados. Os dados do centro de pressão (CoP) foram quantificados usando tridimensional (3D: número de alta densidade e alta velocidade regiões, distâncias médias e máximas entre regiões), bidimensional (2D: área elíptica, velocidade média) e unidimensional (1D: padrão, velocidade). Resultados: Análise de variância Revelou um efeito de interacção significativo entre a tarefa * grupo 1D (F₁₂.2₃₈=3.496, p<0.001), 2D (F₆.₃₈₄=11.472, p=0.004) e os parâmetros 3D (F₁₂.2₃₈=2.5₄₃, p=0.00₄). Efeitos univariados significativos foram observados para todos os parâmetros, com maiores valores de balanço corporal sob restrições visuais e biomecânicas, separadas ou combinadas. Conclusões: Os pacientes com SCA3 apresentaram estratégias de movimento comparadas com indivíduos saudáveis, aumentando o balanço do corpo sob condições biomecânicas e / ou restrições visuais. O mapeamento cinemático tridimensional revelou estratégias de movimento aleatória ou uma estratégia de movimento caracterizada por uma distribuição estocástica de CoP, com alta velocidade de correção para os grandes desvios.

Palavras-chave: Doença de Machado-Joseph; Degeneração estriatonigral; Reabilitação.

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1 INTRODUCTION

Spinocerebellar ataxia type 3 (SCA3) is a rare disease characterized by variable degrees of ataxia, pyramidal dysfunction, peripheral neuropathy, ophthalmoplegia, and thus movement disorder [1]. Patients with SCA3 have important balance impairment and high risk of falls that influence their daily living functionality. Factors associated with a higher fall frequency include the severity of ataxia, the presence of pyramidal symptoms, the disease duration, the total number of non-ataxia symptoms, and the genotype of SCA3 [2,3]. Standards of care in SCA3 include exercise and physiotherapy programs [1,4-6] and therefore impairments in postural control must be clearly recognized for the elaboration of a personalized, effective rehabilitation program [7].

Most measures for assessment of postural control comprise qualitative instruments with poor psychometric properties for measuring balance [8]. Force platform stabilometry has been used for the quantitative assessment of postural balance based on the register of center of body pressure (CoP). The dynamics of CoP data reflects the neuromuscular response to movements of the center of body mass [9]. Several parameters are available for a reliable analysis of CoP data including one- and two-dimensional parameters [10-15], in the sense that the large these parameters are the worse the postural control [16]. However, little is known about the movement strategies of patients with SCA3 using this technique; previous studies [17-19] confirm the impaired postural control whilst reinforce the role of stabilometry as a quantitative technique for assessing their postural balance, as well as the effect of rehabilitation programs [6]. Nonetheless, these previous studies lack detailed description regarding the movement strategies adopted by SCA3 patients for maintaining balance. Because the pathophysiology of cerebellar damage typically results in increased body sway and is specific depending on lesion location [20], it is necessary to understand how patients with SCA3 cope with visual and biomechanical demands.

The spatial mapping method was recently developed for location of either CoP displacement or velocity at the base of support area. The mapping of CoP displacement on the 3D-statokinesigram (3D-SKG) [11,15] was linked to the coexisting movement strategies predominantly adopted for maintaining postural steadiness in the upright position: the ankle or hip strategies [21-23]. Conversely, the mapping of CoP velocity on the 3D-statokinemogram (3D-SKMG) [13] was linked to the role of velocity information for postural control [24]. Differently from 1D and 2D parameters that only surrogate information about overall body sway, 3D parameters convey novel information about the predominantly adopted movement strategy [11] and to what extent velocity information plays a major role for maintaining postural stability [13]. That information was not yet reported in patients with SCA3 nor compared to healthy subjects. Therefore, this study investigated the movement strategies for postural control in patients with SCA3 under different combinations of visual and biomechanical demands in the undisturbed upright stance using force platform stabilometry.

2 MATERIAL AND METHODS

2.1 Ethics and participants

The institutional Ethics Committee approved this study before its execution (no. 21.045.2013). The study protocol was explained to the volunteers and all enrolled participants gave their written informed consent before admission.

This is a balanced case-control study (Table 1). Twelve patients with SCA3 were invited to participate in this study and were submitted to a neurological examination for determination of the inclusion criteria: clinical manifestations of cerebellar ataxia with axial predominance and genetic exam confirmatory of SCA3. Exclusion criteria comprised musculoskeletal or cardiorespiratory affections that could compromise gait performance (n=1), pain referral during gait (n=2), utilization of auxiliary equipment for gait (n=2), or medications that interfere in postural control (n=2). Vestibular disorders, large-fiber polyneuropathy and other major causes of postural imbalance were ruled out by electoneuromyography and nystagmography. Five patients with SCA3 completed the stabilometric assessment. All patients used palliative medication (e.g. antidepressant, analgesic) referred by the attending physician and were regularly performing physical and speech rehabilitation. Five members of the academic community were invited to participate in this study and were subjected to a physical examination to allow matching age, body mass, and body height—major confounders of stabilometric analysis [25,26].

2.2 Study protocol

This study followed technical recommendations...
for the assessment of postural balance using force platforms [27]. Participants were asked to step up on the platform barefooted and to maintain their arms hanging at their sides while staying ‘as quiet as possible’. Signal acquisition started 15 s after stepping up on the platform to avoid artifacts due to transients and was automatically finished 30 s after this period. This trial duration was chosen due to the report that patients with SCA3 have difficulties to complete 60-s trials [18,19] and is yet acceptable for obtaining reliable results [14,27]. Each participant performed three trials of four different postural tasks characterized by visual and/or biomechanical demands: feet apart (acromion-to-acromion distance) with eyes open (FAEO) or eyes closed (FAEC); and feet together (touching heels and toes) with eyes open (FTEO) or closed (FTEC). The sequence of postural tasks within each trial was randomized using random numbers generators (www.random.org) considering first the visual condition and then the feet position. During EO tasks the participants were instructed to focus on a small object fixed at the eye-level on a wall 1.5 m apart from the force platform. After two trials the participants were allowed to move freely or rest during 60 s while waiting for the next trial.

2.3 Signal acquisition and processing

The methods for signal processing and spatial mapping for generation of 3D-SKG and 3D-SKMG were described in details elsewhere [11,13]. Briefly, raw signals were acquired at 100 Hz from the analog channels of the force platform (AccuSway Plus, AMTI, USA), digitalized by a 16-bit converter (NI-USB 6210, National Instruments, USA) and stored for off-line processing. Calculation of forces, moments of force, and CoP coordinates were performed using the calibration matrix and the manual provided by the platform’s manufacturer. CoP coordinate values had their mean value subtracted on both axes before digital filtering by a 2nd order low-pass Butterworth filter (cutoff frequency of 2.5 Hz) in direct and reverse direction.

The 3D-SKG is a bivariate histogram in the XY plane (X-axis: mediolateral; Y-axis: anteroposterior) of CoP coordinates sampled in bins sized 1x1 mm. Each bin stores the cumulative sum of CoP x,y coordinates that visited it during the postural task such that high bin counts represent high-density regions [11]. Likewise, the 3D-SKMG is a bivariate map of CoP speed in the XY plane sampled in the same bin. Each bin stores the cumulative sum of CoP speed in which it was visited, averaged over time such that high bin values represent high-speed regions [13]. In sequence, a 3x3 median spatial filter is applied to smooth both 3D-SKG and 3D-SKMG before dichotomization using percentile and speed thresholds, respectively. Finally, a two-scan connected-component labeling algorithm located and counted the number of regions in each map.

2.4 Stabilometric parameters

The number of high-density regions (nHDR) was obtained from the 3D-SKG [11]. The following variables were obtained from the 3D-SKMG: the number of high-speed regions (nHSR); the average distance between all regions and the center of the CoP area (Davg); and the maximal distance between all regions and the center of the CoP area (Dmax) [13]. Representative parameters from one-dimensional (1D) stabilograms were also computed in X-axis and Y-axis [16]: standard deviation (SDX; SDY) and maximum velocity (Vmax X; Vmax Y). Finally, parameters from the two-dimensional statokinesigrams (2D-SKG) were computed in the XY plane: elliptical area (Area PCA) [28] and the average velocity (Vavg).

2.5 Statistical analysis

Values are shown as mean±SD, median [minimum; maximum], and absolute frequency (%) depending on the variable type. The average of the three trials was used for summary statistics and all subsequent analyses. Multivariate analysis-of-variance (MANOVA) was used followed by the Dunnett’s t post-hoc test to test for main and interaction effects among the factors group (SCA3, healthy; control: healthy), task (FAEO, FAEC, FTEO, FTEC; control: FAEO), and trial (#1, #2, #3; control: #1) independently for 1D, 2D, and 3D parameters. Wilk’s λ, η² values and F-test values were reported alongside a statistical significance level of p<0.05. Statistical analysis was conducted with SPSS 22 (IBM Inc., USA).

3 RESULTS

All participants completed the trials for each postural task investigated, except patient #3 who could not perform FTEC trials. Figure 1 shows the stabilometric plots in all postural tasks for a representative patient. It can be noticed an increase in CoP displacement area among more demanding postural tasks in the 2D-SKG (left column, top to bottom rows). It can also be noticed an increase in the number of high-density regions in the 3D-SKG (middle
column), as well as an increase in the number and spread of high-speed regions in the 3D-SKMG (left column), both information otherwise not noticeable in the 2D-SKG.

Table 2 shows a trend to increase the values of all stabilometric parameters with the increasing postural demand on tasks from FAEO to FAEC, FTEO, and FTEC. Significant multivariate interaction effect was not observed among group*task*trial regarding 1D (λ = 0.743, η² = 0.072, p = 0.271), 2D (λ = 0.926, η² = 0.038, p = 0.839) or 3D parameters (λ = 0.816, η² = 0.049, p = 0.754). Significant interaction effect was found between group*task for 1D (λ = 0.651, η² = 0.133, F₁₂,238 = 3.496, p < 0.001), 2D (λ = 0.530, η² = 0.272, F₆,184 = 1.147, p < 0.001), and 3D parameters (λ = 0.727, η² = 0.101, F₁₂,238 = 2.543, p = 0.004), whereas no interaction effect was significant between trial*group (1D: λ = 0.899, η² = 0.052, p = 0.286; 2D: λ = 0.967, η² = 0.017, p = 0.535; 3D: λ = 0.964, η² = 0.018, p = 0.913) or trial*task (1D: λ = 0.780, η² = 0.060, p = 0.509; 2D: λ = 0.935, η² = 0.033, p = 0.899; 3D: λ = 0.775, η² = 0.062, p = 0.471). Significant main effect were observed for group in 1D (λ = 0.464, η² = 0.536, F₄,90 = 25.967, p < 0.001), 2D (λ = 0.630, η² = 0.370, F₂,90 = 27.070, p < 0.001) and 3D parameters (λ = 0.491, η² = 0.509, F₄,90 = 23.343, p < 0.001), as well as for task in 1D (λ = 0.441, η² = 0.239, F₁₂,238 = 7.200, p < 0.001), 2D (λ = 0.504, η² = 0.290, F₆,184 = 12.537, p < 0.001) and 3D parameters (λ = 0.472, η² = 0.221, F₁₂,238 = 6.517, p < 0.001). Conversely, significant multivariate effect was not observed for trial on 1D parameters (λ = 0.944, η² = 0.028, F₈,180 = 0.659, p = 0.727), 2D parameters (λ = 0.971, η² = 0.015, F₄,184 = 0.683, p = 0.604) or 3D parameters (λ = 0.884, η² = 0.060, F₈,180 = 1.436, p = 0.184) thus showing no trend to change their values among the trials.

Increasing values of parameters were observed when visual and biomechanical constraints were applied both separately and combined. Significant univariate interaction effects for group*task were observed for all-but-one parameters: SDX (F₃,93 = 10.310, p < 0.001), SDY (F₃,93 = 12.020, p < 0.001), Vmax X (F₃,93 = 6.704, p < 0.001), Vmax Y (F₃,93 = 3.000, p = 0.035), Area PCA (F₃,93 = 16.678, p < 0.001), Vavg (F₃,93 = 6.844, p < 0.001), nHDR (F₃,93 = 6.404, p < 0.001), Davg (F₃,93 = 7.295, p < 0.001) and Dmax (F₃,93 = 8.432, p < 0.001), except nHDR (F₃,93 = 2.280, p = 0.084). Significant differences were detected in all parameters comparing the most challenging task with the reference one (FTEC → FAEO); most parameters presented significant differences with less demanding postural tasks.

4. DISCUSSION

The major outcomes of this study investigating the movement strategies for postural control in patients with SCA3 comprised: i) patients presented increasing body sway as postural tasks became more demanding by biomechanical and/or visual constraints; ii) stabilometric parameters were affected by the postural task under investigation, with different univariate effect strength; and iii) the spatial mapping revealed distinct postural control strategies in SCA3 patients as compared to healthy subjects. This is the first study to compile information from 1D, 2D and 3D stabilometric parameters for a better explanation about the movement strategies used by patients with SCA3. Whilst the overall effect of the 1D and 2D parameters was also captured by the 3D ones, both the 3D-SKG and 3D-SKGM revealed that different movement strategies were used by patients with SCA3 to maintain postural balance in the undisturbed upright stance. Most importantly, the spatial mapping unveiled how these strategies might change under more demanding postural tasks.

The increasing trend in body sway as more demanding postural tasks are performed was an expected outcome since it is a known effect for healthy adults [10,16] and was previously observed in patients with SCA3 with respect to the visual constraint only [17,18, 29]. It is established that complete visual input allows better postural adjustments and that a large base of support increases stability in older adults [10-17]. Nonetheless, our study not only reaffirmed the role of vision for postural control in SCA3 patients but also systematically demonstrated the effect of narrowing the BoS, which was not reported yet in this population.

The analysis of 3D-SKG revealed that patients presented nHDR≤1 under the less demanding task, which is a movement strategy fairly similar to healthy subjects if the larger CoP displacement is ignored. Our previous study [11] showed that both young and elderly healthy adults predominantly presented nHDR≤1 under both FAEO and FAEC tasks, but they changed their movement strategy (nHDR≥2) only with the more demanding constraints as reported in this study. However, patients with SCA3 increased their nHDR up to 7 under FAEC, a much different movement strategy from that adopted by healthy subjects. Bimodal distributions of CoP data were observed in
patients with unilateral loss of vestibular function [30]. Those data suggest that under visual constraints some movement strategy (e.g. the ankle or hip strategy) was already required and predominantly adopted for maintaining postural balance. Most importantly, the change from single-, double-, or to multi-centered patterns suggest that the more demanding the postural task is the more difficulties the patients has to optimally return their center of mass to the center of the base of support.

The direction of the CoP movement depends on which area of the cerebellum was affected by the lesion, with multidirectional movements observed in patients with lesions of the flocculonodular lobe [20]. It because the cerebellum acts in the online sensory control of the upper body [31]. Also, patients with SCA3 present lesions at the basal ganglia, pontine and cranial nerve nuclei, and spinal neurons in addition to the cerebellar degeneration [1,2]. Collectively, this strongly suggests that they most likely used random movement strategies or even a unique movement strategy – characterized by a stochastic CoP bivariate spatial distribution – that ultimately lead to a augmented body sway area.

The analysis of 3D-SKMG showed complementary, interesting findings to the 3D-SKG. Whilst the increase in nHSR under more challenging postural tasks suggests that movement strategies were more often required for redirecting the center of mass to the center of the base of support, the increase in Davg and Dmax provided evidence that these turning regions were at large distances from the center of base of support. These results are in agreement with our previous study [13] reporting that healthy adults showed predominantly nHSR≈1 nearly centered at the CoP area under FAEO, and more challenging postural tasks (FTEC) increased the nHSR as well as the Davg and Dmax. Our data also show that patients with SCA3 presented distinct velocity-based movement strategies since they increased the nHSR (≈6, maximum=12) under FTEC, whilst healthy subjects showed an averaged nHSR≈2 (maximum=4).

The analysis of the distance among high-speed regions reinforces the differences in movement strategies adopted by patients with SCA3; these patients showed augmented values of group-averaged Davg (5.0 to 19.9 cm) and Dmax (7.0 to 33.7 cm) with more demanding postural tasks that were much higher than those observed for the healthy group (Davg: 2.5 to 4.7 cm; Dmax: 3.4 to 7.0 cm). Because high CoP velocities near the boundaries can be useful to redirect the center of mass toward the egocentric reference of posture, our results suggested that motor responses were most frequently used by SAC3 patients to maintain postural balance, particularly in more demanding postural tasks. Finally, the observation that the cerebellum plays a critical role in generating anticipatory postural adjustments [20] is supported by our results. CoP velocity information – i.e. the time derivative of CoP displacement – may be interpreted as a predictive variable of the displacement of the center of mass, indicating not only the direction but also the magnitude of such displacement [9,32] that are both captured by the 3D-SKMG analyses. Future studies should investigate whether there is a relationship between the parameters from the 3D-SKMG and the ability to perform anticipatory postural adjustments in patients with SCA3 and spinocerebellar ataxia in general.

Most clinical trials in patients with SCA applied balance training among other exercises [4-7]. Rehabilitation programs focused in improving postural balance might be personalized if the results from 3D-SKG and 3D-SKMG are available. Therefore, randomized clinical trials on rehabilitation programs using force platform stabilometry for assessment of postural balance are thus encouraged to investigate to what extent the potential benefits of personalized rehabilitation programs are captured by 3D parameters. Particularly, training anticipatory postural adjustments could be used as a major strategy for rehabilitation of people at high risk of falling. It is also encourage to use nHDR, nHSR, Davg and Dmax to detect improvements in postural balance in future studies for assessment of risk of fall in this population.

Some limitations are worth noticing for a comprehensive interpretation of our findings. The studied sample consisted of patients with severe SCA3 and thus generalization of these results to those with mild SCA3 or other spinocerebellar ataxia genotypes should be cautious. Although our sample was the largest one to perform systematically the most commonly used postural tasks for assessment of postural control [10] and is similar to previous studies in spinocerebellar ataxia [6], our data provide difference values for planning larger randomized clinical trials on rehabilitation programs focusing on postural balance outcomes based on force platform stabilometry. Conversely, major strengths of our study comprise the inclusion of healthy participants matched for major confounders of postural balance. Moreover, the advanced computational methods we used for calculation of 3D stabilometric pa-
rameters alongside the well-known 1D and 2D analyses were not applied in those previous studies and were required for a novel interpretation of stabilometry data. Finally, by adhering to technical recommendation [27] we expected to improve the clinical application of our results and to contribute to future systematic reviews on this subject.

5. CONCLUSIONS

Patients with SCA3 presented augmented movement strategies that differ from healthy subjects, characterized by increasing body sway as the undisturbed postural tasks becomes more demanding by biomechanical and/or visual constraints as measured from 1D and 2D parameters. Kinematic mapping showed that the increased body sway is related to either random movement strategies or a unique movement strategy characterized by a stochastic CoP distribution, using high speed to correct for large body sway deviations.

ACKNOWLEDGEMENTS

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CONFLICTS OF INTEREST

None.

REFERENCES

Table 1. Clinical characteristics and anthropometrics data of patients with spinocerebellar ataxia 3 and healthy participants (n=5 each).

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*Two-sample, two-tailed, unequal variance t-test. NT: not tested.*
Table 2. Results of the stabilometric test (n=5 for each group).

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<td>[1;2]</td>
<td>[1;6]</td>
<td>8&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Postural</td>
<td>[1;3]</td>
<td>[1;3]</td>
<td>[1;4]</td>
</tr>
<tr>
<td></td>
<td>Dmax (cm)</td>
<td>7.0±6.3</td>
<td>14.7±14.1</td>
</tr>
</tbody>
</table>

<sup>AB</sup>Statistically different from control postural task (feet apart eyes open).
Figure 1. Stabilometric plots in all postural tasks for a representative patient.