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Plasticity of static graviceptive function in patients with cervical dystonia

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ABSTRACT

Objective: Botulinum toxin (BoNT) is effective in improving abnormal head posture in cervical dystonia (CD) within a period of several weeks to an upright position. These dynamic alterations over time represent a unique model to study the plasticity of static graviceptive function in CD by assessing the subjective visual vertical (SVV).
Methods: SVV was assessed in 30 CD patients and 13 controls, in their habitual head posture and with fixed head positions at different angles of head tilt. The patients were tested before and 3 weeks after BoNT administration.
Results: At baseline, the patient's estimates in their habitual head posture and at forced head tilt angle of 30° differed significantly from those of controls. This effect was no longer visible after BoNT injection, or when the patient's head was fixed in an upright, and at a 15° head tilt position, respectively. A moderate positive correlation between disease severity and SVV aberrations was found. When comparing within-group changes, in all participants significant aberrations occurred when the head was tilted at 30°, which may be explained by the physiological E-effect.
Conclusion: Our findings demonstrate that patients with CD exhibit altered static graviceptive perception when tested in their habitual head posture and an overshooting E-effect at the major forced head tilt of 30°. This graviceptive perceptual deficit can be reversed by modification of the somatosensory input (i.e. head fixation) as a short-term effect, and by changes in the proprioceptive input (i.e. BoNT injections) as a long-term effect.

1. Introduction

The evaluation of verticality perception is usually performed by the assessment of the SVV, in healthy individuals with a maximum aberration of <2° from the 'true' gravitational vertical [1,2]. Major aberrations of the SVV, up to 10–30° in the direction of tilt, can be produced by a body tilt of 80–90° to one side, which is also referred to as the "A-effect" [1]. Lateral head and body tilt up to 50° leads to perception of the SVV overshooting to the opposite side of the tilt, which is called the "E-effect" [3–6]. In healthy persons, small head roll angles (under 30°) revealed more accurate estimations, close to the gravitational vertical [2]. Verticality perception is mediated by visual, otolithic and somatosensory input [1]. Thereby, the somatosensory system and proprioceptive input from neck muscles, respectively play a major role in the estimation of the SVV during lateral body tilt [1,7–10].

The pathophysiological mechanism of CD still remains unclear. Animal models suggest involvement of multiple cerebral integration centers. The "sensory trick", supports the assumption of altered sensorimotor processing in CD. In addition, vestibular abnormalities have been suggested [11,12]. Previous studies on the perception of verticality in CD yielded conflicting results [7,13,14]. When treated with BoNT by an experienced clinician, head posture in people with CD usually improves within a period of 3 weeks to an upright position and diminishes subsequently after approximately 9 weeks. These dynamic alterations of head posture over time represent a unique model to study the effects of altered somatosensory and otolithic input on the perception of verticality. In this study we tested the SVV of CD before and after BoNT, in order to evaluate the plasticity of static graviceptive function in these patients. The purpose of the present study was to 1) assess static graviceptive function at habitual head posture and at different head tilts (i.e. short-term modulation of the somatosensory input) in normal subjects and in patients with CD and

2) study the effects of BoNT injections (i.e. long-term modulation of the proprioceptive input) on static graviceptive function in patients with CD.

Abbreviations: AIC, Akaike information criterion; BoNT, botulinum toxin; CCW, counter clockwise; CD, cervical dystonia; CI, confidence interval; CNS, central nerve system; CW, clockwise; P, p-value; SD, standard deviation; SVV, subjective visual vertical.

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2. Materials and methods

2.1. Subjects

32 consecutive patients with idiopathic CD undergoing regular treatment with BoNT at the BoNT Outpatient Clinic of the Department of Neurology, Medical University Vienna, were included in the study. All patients participated at baseline evaluation, however, two patients refused to complete the follow-up examination (3 weeks after baseline evaluation), so that a total of 30 patients completed the whole study (mean age 59 [SD 12] years; females 19, 63.3%). The patient's clinical details are listed in Table 1.

At baseline, 17 (56.7%) patients presented with habitual head deviation (chin-nasion line rotated in the roll plane) to the right, and 13 (43.3%) to the left, respectively. Patients with a history of vestibular disorders, as well as patients with head rotation in the horizontal plane exceeding 15° or secondary CD were excluded.

2.2. Standard protocol approval and patients consents

The study was approved by the ethical committee of the Medical University of Vienna. All patients and controls signed an informed consent prior to their inclusion in the study. The study has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki. This pilot study has been registered at http://clinicaltrials.gov (NCT01180270).

2.3. Procedures

Patients were treated with four different preparations of BoNT (Table 1). The median interval between first SVV assessment at baseline and previous BoNT injection was 105 days (range 83–371). The severity of CD was assessed by the Tsui score, head deviation was measured by referencing the chin-nasion line to earth vertical with a finger goniometer (KaWe Germany) [15]. In order to rule out vestibular disorders, which might interfere with SVV perception, such as vestibulopathy or neuritis vestibularis, all patients underwent vestibular- and ocular motor function tests by means of digital videooculography and a rotational chair system (System 2000, Micromedical Technologies, Illinois, USA) at their baseline visit.

Table 1
Clinical details of 32 patients at baseline assessment.

	N (%)	Median (IQR)
Male	11 (36.7)	
Female	19 (63.3)	
Age in years (a)	30 (100)	59.0 (12.0)
Duration of disease (a)	30 (100)	15.6 (9.4)
BoNT treatment duration (a)	30 (100)	9.4 (7.0)
Severity of disease measured by Tsui score	30 (100)	6.2 (3.9)
Predominant head deviation in degrees (°)		
Clockwise head deviation	17 (56.7)	10.0 (4.8)
Counterclockwise head deviation	13 (43.3)	8.5 (7.7)
Amount of BoNT preparation applied in MU		
Abo-BoNT A, Dysport®, Ipsen	14 (46.7)	579.8 (233.0)
Inco-BoNT A, Xeomin®, Merz	7 (23.3)	149.6 (59.6)
Ona-BoNT A, Botox®, Allergan	8 (26.7)	212.8 (93.4)
Rima-BoNT B, NeuroBloc®, USWorldMed	1 (3.3)	15,500
Patients with CNS-active co-medication		
Total	12 (40.0)	
Antidepressant	9 (30.0)	
Anticonvulsants	4 (13.3)	
Anticholinergics	2 (6.7)	
Musclerelaxants	1 (3.3)	
Neuroleptics	0	

BoNT: botulinum toxin; MU: mouse units; N: number of patients; SD: standard deviation.

Assessment of SVV, Tsui score and head deviation was performed at the baseline visit directly before routine BoNT treatment (i.e. at time of minimum treatment effect). Three weeks after injection (median 21 days, range 18–28), i.e. at time of maximum treatment response, the initial assessment was repeated. As controls, 13 healthy subjects (age 52.8 [11.6], nine females, 69.2%) without a history of vestibular disorders, with normal vestibular- and ocular motor function tests (System 2000, Micromedical Technologies, Illinois, USA) and no history of CNS-active medications participated in the study.

2.4. Assessment of SVV

SVV was assessed in an upright sitting position in a completely dark room. In front of the participants, at a distance of 100 cm, there was a dim light bar, 2 mm wide and 10 cm long, which could be rotated about its midpoint by means of an electronic motor and a remote control device (System 2000, Micromedical Technologies, Illinois, USA). All participants adjusted the bar six times from randomized starting positions for parallel alignment with the perceived gravitational vertical. The six estimates were averaged for further analysis. SVV alignments were performed both by patients and healthy controls at five different head positions (head fixed upright 0°, CW and CCW: fixed head deviation at 15° and fixed head deviation at 30°). A plastic head ring and a hook-and-loop tape that was mounted on an adjustable neck rest (which covered the occiput and the posterior neck) fixed the head. All patients and controls also performed one trial with habitual head posture. The interval between each test/head position was approximately 3 min.

2.5. Statistical analysis

Categorical variables are given as absolute numbers and percentages; continuous variables are given as median and interquartile-range (IQR). SVV was measured in degrees of deviation from gravitational vertical. CCW deviations were calculated as negative values, CW deviations as positive. For the evaluation of differences in the perception of verticality in CD patients and healthy controls the direction of SVV deviations has not been taken into account, i.e. that absolute deviations from earth vertical - irrespective of their direction - were calculated. Controls were assessed once, as no injections were performed, and the median aberrance of the SVV at 0° was very small at baseline measures.

For comparison of differences between patients and controls, fixed head positions and visits, repeated measures ANOVA was applied: In the model only for patients deviations, the visits and the interaction of the fixed head positions were included. Two separate models for each visit compared patients with controls (including fixed head positions, deviations of patients and controls, and the interaction). The last model compared the deviations of controls. Covariance structure was selected minimizing AIC. In addition, *t*-tests or Wilcoxon-tests, depending on the distribution of the respective continuous variable, were used. Pearson correlation was used to measure the association between Tsui score and SVV aberrations. Boxplots and scatter-plots were generated to visualize distributions. A two-sided $p < 0.05$ was considered statistically significant. The statistical analysis was performed with the SAS system version 9.2 (2008; SAS Institute Inc., Cary, NC).

3. Results

3.1. Absolute SVV deviations at habitual head position

Absolute SVV-deviations from true gravitational vertical were calculated irrespective of CW- or CCW direction. At baseline, all CD patients presented with marked abnormal habitual head posture, were reflected by elevated Tsui scores (Table 1). SVV judgments of patients tested without head fixation, i.e. at their “habitual” head position, yielded major aberrations of SVV from earth vertical. The median SVV