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SHORT COMMUNICATION

Postural control in episodic ataxia type 2: no evidence for increased vestibular excitability

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Abstract

Background and purpose: Patients with episodic ataxia type 2 (EA2) suffer from recurrent paroxysmal episodes of vertigo and oscillopsia. Pathophysiologically, altered neuronal excitability has been suspected. Vestibular excitability in 22 EA2 patients and 22 age-matched healthy participants was compared.

Methods: Galvanic vestibular stimulation (GVS) was used to assess vestibular excitability by vestibular motion perception thresholds and mean postural sway velocity during various visual and proprioceptive conditions in the two groups. Control stimuli using sham and no GVS were established to identify the specificity of GVS-induced postural sway.

Results: In the baseline condition, EA2 patients showed larger postural instability. However, motion perception thresholds and the increase in mean postural sway velocity during vestibular stimulation (stimulation ratio) did not differ between groups. Postural sway during suprathreshold GVS increased with the vestibular motion perception threshold in EA2 patients, in contrast to healthy participants.

Conclusions: The larger postural unsteadiness of EA2 patients probably reflects their progressive cerebellar degeneration. It is not related to abnormal visual (Romberg's ratio) or proprioceptive control of stance. Postural unsteadiness during vestibular stimulation does not indicate altered vestibular excitability in EA2 patients. However, vestibular stimulation increasingly destabilized postural control of EA2 patients with higher motion perception thresholds when proprioceptive information was diminished. This conclusion, however, is restricted to the postural control of EA2 patients in the interval between the vestibulo-cerebellar episodes.

KEYWORDS
episodic ataxia type 2, postural control, vestibular excitability, vestibular motion perception thresholds

INTRODUCTION

Patients with episodic ataxia type 2 (EA2) suffer from a combination of recurrent paroxysmal episodes of unsteadiness lasting minutes to hours with vertigo, oscillopsia (due to cerebellar gaze-holding deficits) and dysarthria as well as slowly progressive ataxia of gait [1] and stance [2, 3]. Genetically, monoallelic disease-causing variants in the *CACNA1A* gene on chromosome 19p13, which encode voltage-gated subunits of the neuronal Cav2.1 P/Q-type calcium channel, may lead to a loss or a gain of function thereby eliciting a change of presynaptic excitability in the cerebellar Purkinje cells [4]. Altered cortical excitability has been shown by spontaneous interictal epileptic discharges in EA2 patients using electroencephalogram recordings [5].

Episodes in EA2 are typically triggered by physical exertion and sports activities which naturally involve head movements, that is, vestibular stimulation. Therefore, an increased vestibular excitability in EA2 was suspected and the hypothesis that experimental vestibular stimulation using galvanic vestibular stimulation (GVS) destabilizes postural control of EA2 patients more than that of age-matched healthy control participants (HCs) was tested. Using posturography, larger mean postural sway velocity (PSMV) of EA2 patients during GVS perturbations was hypothesized, in addition to the larger baseline unsteadiness resulting from chronic cerebellar degeneration. The authors are not aware of any previous posturographic study on EA2 patients comparing the stabilizing stance of different sensory components.

METHODS

Twenty-two EA2 patients and 22 age-matched HCs were enrolled in this study. Patients were recruited from the Department of Neurology, University of Lübeck, and some other centers for neurodegenerative and cerebellar diseases in Germany (Universities of Duisburg-Essen, Tübingen and Charite Berlin). All patients had pathogenic heterozygous mutations in the *CACNA1A* gene. Nearly all of them reported that vertigo attacks were triggered by physical exercise (85%), stress (90%) or caffeine (38.9%). Age-matched HCs had no history of vertigo, dizziness, migraine or other types of balance disorders. Demographics and patient characteristics are summarized in Table 1. On clinical examination between the vertigo attacks, patients exhibited gaze-evoked nystagmus in 55% (35% of them with downbeat nystagmus), head-shaking nystagmus in 27%, saccade dysmetria in 50%, abnormal horizontal and vertical smooth pursuit in 77% of patients. The majority (86%) showed ataxia of gait and stance and limb ataxia was found in up to 64%. Subjective visual vertical was normal in both groups. The mean gain of the vestibulo-ocular reflex was lower in the patient group (Table 1). Some of the patients were on 4-aminopyridine (Fampyra™ 20 mg/day; 18% of patients) or acetazolamide (250–500 mg/day, 27% of patients); 45% of the patients were unmedicated. Clinical exclusion criteria included dementia, major depression, personality disorders, polyneuropathy, usage of sedative drugs, consumption of alcohol and the inability to stand without assistance.

Posturography was performed using the wearable APDM's Mobility Lab System™ (Portland, OR, USA) and GVS (DS5 model, Digitimer Ltd, UK) was used as described recently [8]. Individual vestibular motion perception thresholds were obtained by applying 10 s of 1 Hz alternating stimulation, that is, low frequency alternating current which passed between the two mastoid electrodes [6]. The following four stimulation conditions were used: (i) no current (no GVS), (ii) a low current (0.5 mA, low GVS), (iii) a high intensity current (1.5 mA) above the perceived threshold (high GVS) and (iv) a sham stimulus (sham GVS) employing a short

TABLE 1 Demographics and clinical scores of the participants including disease duration and clinical scores of cerebellar, cognitive and vestibular function.

	Patients	Controls	Level of significance
Age (years)	41.5 ± 13.9	41.1 ± 13.8	n.s.
Age at diagnosis (years)	33.9 ± 15.9	–	–
Disease duration (years)	10.5 ± 6.0	–	–
Attacks/month	5.0 ± 6.4	–	–
Attack duration (h)	4.3 ± 3.9	–	–
SARA	4.73 ± 3.64	0.05 ± 0.21	<0.001
INAS	5.52 ± 3.14	1.14 ± 1.62	<0.001
DHI	39.62 ± 25.32	-	-
MoCA	25.14 ± 3.45	28.32 ± 2.06	0.001
Nine-hole PEG test (s)	21.24 ± 3.3	17.57 ± 1.74	<0.001
SVV	0.37	−0.44	n.s.
vHIT	0.85 ± 0.27	1.01 ± 0.11	0.022
Vestibular perception threshold	0.46 ± 0.30	0.38 ± 0.12	n.s.

Note: Perceptual values of vestibular motion perception thresholds by galvanic vestibular stimulation [6] and the gain of the vestibulo-ocular reflex by quantitative head impulse test using vHIT [7] are also given.

Abbreviations: DHI, Dizziness Handicap Inventory; INAS, Inventory of Non-ataxia Signs; MoCA, Montreal Cognitive Assessment; n.s., not significant; SARA, Scale for the Assessment and Rating of Ataxia; SVV, subjective visual vertical; vHIT, video-oculography.

ramp of 100 ms with the low intensity current followed by 400 ms without stimulation [9].

Each GVS stimulus was examined once in each experimental condition, with the eyes open during fixation of a gaze straight ahead target (at 1 m) and with the eyes closed in each experimental condition (20 s each). A four (2 × 2 × 4 × 2) factorial study design was used to study PSMV with the factors VISION (eyes open, eyes closed), SOMATOSENSORY (firm platform vs. foam), STIMULATION (no GVS, low GVS, high GVS and sham GVS) and GROUP (EA2 vs. HCs). VISION, STIMULATION and SOMATOSENSORY were taken as within-subject factors (repetitive runs) and GROUP (EA2 vs. HCs) as a between-subjects factor using multi-factorial ANOVA. The stimulation ratio was calculated by dividing PSMV during GVS by PSMV during no GVS. Statistical analyses were performed with SPSS (22.0.0.2; IBM Corp., Somers, NY, USA). Significance levels of post hoc tests were Bonferroni corrected for multiple testing. Correlation analyses were performed using the Spearman rho coefficient. The PSMV of participants is displayed (in mm/s ± SEM). Romberg's ratio (PSMV with the eyes closed/eyes open) was calculated as described previously [10].

RESULTS

There was no significant difference of vestibular motion perception (by GVS) between EA2 patients compared to HCs (Table 1). Generally, there were main effects of VISION ($F(1, 39) = 47.033$, $p < 0.001$), SOMATOSENSORY ($F(1, 39) = 70.807$, $p < 0.001$), STIMULATION ($F(3, 37) = 17.843$, $p < 0.001$) and GROUP ($F(1, 39) = 8.056$, $p = 0.007$), that is, patients showed larger PSMV but largely irrespective of the experimental variables. There were significant interactions of VISION × SOMATOSENSORY ($F(1, 39) = 51.732$, $p < 0.001$), VISION × STIMULATION ($F(3, 38) = 12.628$, $p < 0.001$), SOMATOSENSORY × STIMULATION ($F(3, 38) = 17.441$, $p < 0.001$) and a triple interaction for VISION × SOMATOSENSORY × STIMULATION ($F(3, 37) = 9.276$, $p < 0.001$). There was an interaction of GROUP × VISION ($F(1, 39) = 5.248$, $p = 0.027$) and GROUP × VISION × SOMATOSENSORY ($F(1, 39) = 4.536$, $p = 0.04$), that is, the PSMV of patients was larger on eye closure ($p < 0.007$), both on the firm platform ($p < 0.021$) and on foam ($p < 0.013$) (Figure 1). Importantly, there were no main effects for GROUP of Romberg's ratio (Figure 1b) or the stimulation ratio for the different conditions, that is, patients did not show a larger increase of PSMV during GVS. PSMV increased with higher motion perception thresholds whilst patients were standing on foam with their eyes open during low GVS ($r = 0.428$; $p = 0.047$) and high GVS ($r = 0.448$; $p = 0.037$). This correlation was not found with the eyes closed, on the firm platform or during ineffective GVS (no GVS, sham GVS) nor in HCs. ANOVA revealed no significant differences in PSMV between HCs or patients with and patients without medical treatment (see supplemental material). Furthermore, there were no correlations with any of the postural parameters with disease duration or the clinical scores Nine-Hole- Peg- Test (NHPT) Scale for the Assessment and Rating of Ataxia [SARA], Inventory of Non-ataxia Signs [INAS], Dizziness

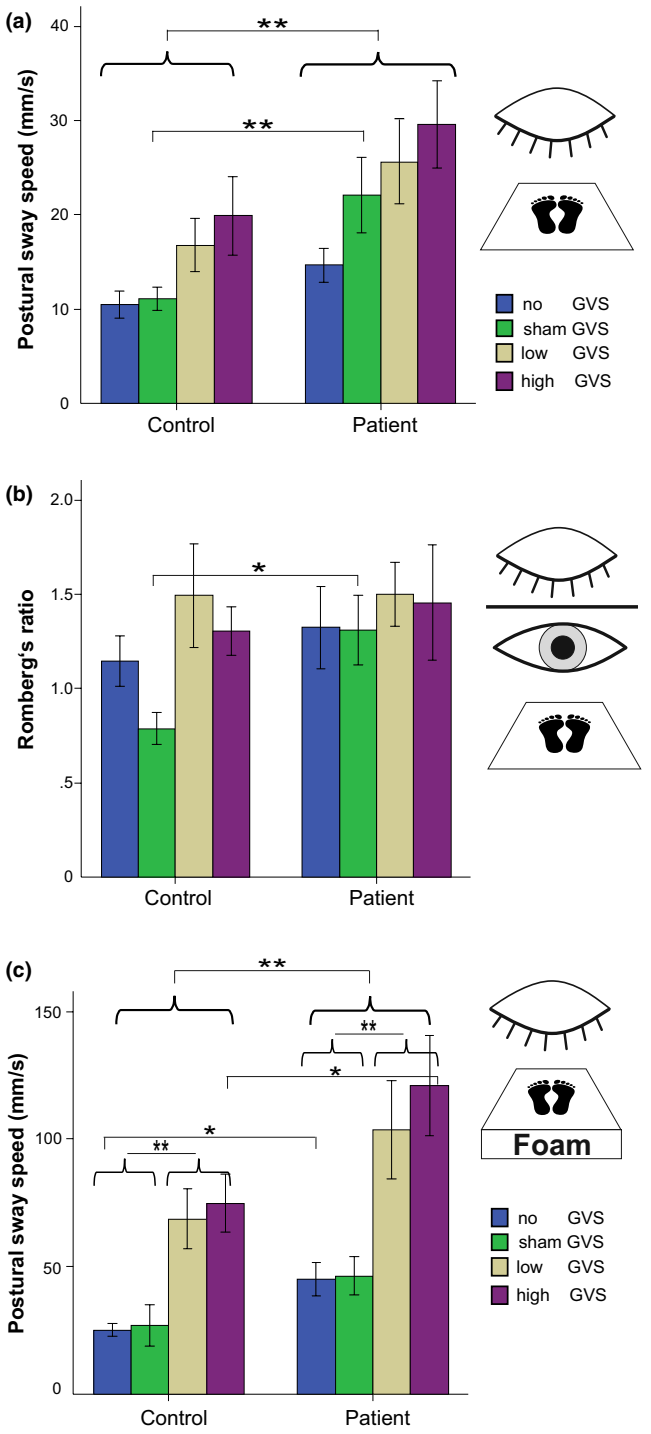

FIGURE 1 Mean postural sway velocity (mm/s ± SEM) of participants (healthy control participants vs. EA2 patients) is shown during no and different modes of galvanic vestibular stimulation (no GVS, sham GVS, low GVS, high GVS, see Methods) on the firm platform (a), (b) and on foam (c) with the eyes closed and for Romberg's ratio (PSMV on eye closure/eyes open). *$p = 0.05$; **$p = 0.01$.

Handicap Inventory [DHI], Montreal Cognitive Assessment [MoCA]) or the vestibular-ocular reflex.

DISCUSSION

Patients of this large EA2 cohort showed a larger postural unsteadiness compared with age-matched HCs, irrespective of the experimental conditions. This postural ataxia probably reflects the progressive cerebellar degeneration in EA2 [1]. Unlike expectations, our data do not support the hypothesis of an increased vestibular excitability in EA2. The hypothesis was based on the following background: (i) the high incidence of EA2 with other channelopathies, for example migraine and epilepsy [11]; (ii) the monoallelic disease-causing variants in the *CACNA1A* gene encode the α1 subunit of the P/Q-type voltage-gated channel Cav2.1 which plays a critical role in the control of presynaptic membrane excitability and neurotransmitter release, especially in the cerebellar Purkinje and granule cells [12, 13]; and (iii) the effective treatment with agents (4-aminopyridine) that restore the normal excitability of cerebellar Purkinje cells [14].

Vestibular excitability was tested on a behavioral and perceptual level. The vestibular motion perception threshold of patients with bilateral vestibulopathy [9] is higher than in HCs and lower, for example, in patients with persistent postural-perceptual dizziness [6]. Importantly, altered motion perception thresholds may account for abnormal postural sway [8]. A larger vestibular excitability was suspected in EA2 patients by lower motion perception thresholds but on average no group differences were found in the thresholds. Postural compensation for vestibular perturbation depends not only on the thresholds of egomotion perception but also on visual and somatosensory feedback signals. Noticeably, despite the lack of group differences, vestibular egomotion perception thresholds seem to affect postural instability in EA2 patients as postural sway increased with higher egomotion perception thresholds when proprioceptive information was diminished. Somatosensory feedback seems to become important for postural compensation during vestibular stimulation in EA patients with larger egomotion perception thresholds. This dependence of posture-stabilizing somatosensory feedback signals on vestibular egomotion thresholds may additionally account for the patients' larger postural instability, apart from cerebellar degeneration in EA2.

On a behavioral level, the abnormally large PSMV of EA2 patients does not seem to be related to abnormal visual control of stance since PSMV without GVS was no different between the groups during eye closure and with Romberg's ratio (Figure 1a,b). Using suprathreshold GVS, both groups showed an increase in PSMV, irrespective of visual control (Figure 1b), which was proportional to the baseline unsteadiness (no group difference in the stimulation ratio). Even in the most difficult postural condition (foam; Figure 1c) the stimulation ratio did not reveal group differences, that is, the larger PSMV during high GVS reflects the higher baseline unsteadiness of EA2 patients (cerebellar degeneration) despite the fact that PSMV was not correlated with the clinical cerebellar (SARA, INAS) and cognitive (MoCA) scores.

Episodic ataxia type 2 is usually associated with non-sense or missense mutations or *CACNA1A* gene deletions that cause loss of channel function [15] but this could correspond to upregulation of other voltage-gated calcium channels [13]. Our EA2 patients used vestibular signals as HCs did which implies normal vestibular excitability, irrespective of the gain of or loss of function nature of the *CACNA1A* mutations [4]. It cannot be explained by a therapeutic effect masking altered excitability as the subgroup of patients who were still on and responsive to fampridine or acetazolamide did not differ in PSMV increase during effective GVS. Moreover, it was not considered that migraine-related mechanisms account for the posturographic findings (see supplemental material).

Our conclusion of normal vestibular excitability is limited to the interval between vestibulo-cerebellar episodes as the patients during an EA2 attack were not examined neither was an attack by GVS elicited in any of the participants. Noteworthy, postural instability of EA2 patients during GVS did not correlate with the number of vestibulo-cerebellar episodes per month. Altered vestibular excitability may be potentially disclosed by studying neural activity in the cerebellum of EA2 patients.

AUTHOR CONTRIBUTIONS

Janina von der Gablentz: Conceptualization; investigation; funding acquisition; writing – original draft; methodology; project administration; formal analysis; resources; validation. **Nina Overbeeke:** Investigation; methodology; formal analysis. **Dagmar Timmann:** Writing – review and editing; resources. **Christos Ganos:** Writing – review and editing; resources. **Matthis Synofzik:** Writing – review and editing; resources. **Norbert Brüggemann:** Funding acquisition; conceptualization; writing – review and editing; methodology; validation; resources; supervision. **Christoph Helmchen:** Supervision; resources; conceptualization; investigation; funding acquisition; writing – original draft; methodology; validation; visualization; formal analysis; project administration. **Andreas Sprenger:** Conceptualization; investigation; writing – review and editing; validation; methodology; software; formal analysis; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The study was approved by the local Ethics Committee of the University of Lübeck (16-068) and written informed consent was obtained from all participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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