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ORIGINAL COMMUNICATION

Vertigo and vestibular abnormalities in spinocerebellar ataxia type 6

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Abstract Spinocerebellar ataxia type 6 (SCA6) is a calcium channelopathy due to a pathological CAG repeat expansion in *CACNL1A4*. Patients frequently describe paroxysmal vertigo early in the disease course, but it is not clear whether this is central or labyrinthine in origin. To address this issue we studied 21 SCA6 patients. Symptoms of vertigo were defined using a structured questionnaire. Signs were recorded during a standardised bed-side vestibular examination that included systematic positional testing with Frenzel goggles.

Brief, recurrent attacks of vertigo occurred in 13 patients, usually preceding the onset of ataxia. Nystagmus was observed behind Frenzel goggles in 14 patients, and was induced either during positional testing, or head shaking in 20 patients. Only one patient had findings typical of benign paroxysmal positional vertigo (BPPV). Combined downbeat and horizontal gaze-evoked nystagmus ("side-pocket") was the most common form, occurring most commonly in supine and head-hanging positions, and following horizontal head-shaking. Nystagmus beating away from the ground (apogeotropic) occurred in 9 patients as they lay on their side.

In conclusion, vertigo and abnormalities on bedside vestibular examination are common in SCA6, with forms of nystagmus typical of cerebellar, rather than labyrinthine, disease. These findings demonstrate phenotypic overlap between SCA6 and episodic ataxia type 2, which are both due to mutations in *CACNL1A4*.

Key words spinocerebellar ataxia · stereopsis · nystagmus · ocular motility · vertigo · vestibular

Introduction

Spinocerebellar ataxia type 6 (SCA6) is a late-onset form of hereditary cerebellar ataxia caused by a CAG repeat expansion in the *CACNL1A4* gene encoding the alpha 1A-voltage-dependent-Ca^{2+} channel subunit on chromosome 19p13.1 [1]. A range of eye movement disorders have been defined in SCA6 [2–4], including impaired smooth pursuit and eye-head tracking, impaired ability to hold eccentric gaze (causing gaze-evoked nystagmus) and downbeat nystagmus, with relatively normal saccades. Whilst studying a large kinship of SCA6 patients, we were impressed by the frequent complaint of vertigo, often predating the onset of ataxia. Prior studies have reported vertigo as a symptom in 12–72 % of SCA6 patients [5–7], but there are no prospective studies using the range of bedside tests that are now a standard part of the vestibular examination. Accordingly, we set out to characterise the nature of the vestibular symptoms and signs in SCA6, and found that almost every patient in our cohort showed clinical signs

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indicating central abnormalities of the vestibular system.

Patients and methods

We studied a group of 21 patients with genetically confirmed SCA6: 7 males and 14 females, with a mean age of 67 years (range 54–85 years). Previous haplotype analysis has shown that all were genetically related and descended from a common founder [8]. All patients gave informed consent in accordance with the declaration of Helsinki. Two observer conducted each phase of the history and examination, and it was necessary for there to be agreement for findings to be recorded. A structured history of vertigo and other causes of dizziness were obtained using a standardised questionnaire, based on current clinical principles [9]. Specific inquiry was made of the nature of the symptoms (i.e., whether the complaint was indeed vertigo), as well as the duration and frequency of attacks, and whether episodes of vertigo preceded the development of ataxia. The effects of head position, posture, fatigue, and environment (e.g., supermarkets) on attacks of vertigo were determined. Associated nausea, sweating, hearing loss, tinnitus, headaches, and migrainous symptoms were also noted. The duration and extent of ataxia, the frequency of falls and current medication were all documented.

Best corrected visual acuity was evaluated with a near card, first with the head still and then as patients made small, 1–2 Hz, head oscillations, horizontally or vertically. Stereopsis was tested using the Titmus test (Stereo Optical, Chicago, IL, USA), with polaroid glasses to separate the stimuli presented to each eye. Any abnormalities of head posture, eyelids, pupils, visual fields or hearing were noted. Blood pressure was recorded, first with the patient supine, and then standing.

The bedside examination of eye movements [4, 9] consisted of: (1) ocular alignment (cover test) during viewing of a far target; (2) visual fixation (3) horizontal and vertical saccades (latency, speed, accuracy, conjugacy); (4) horizontal and vertical smooth pursuit (head stationary) and smooth eye-head tracking; (5) the vestibulo-ocular reflex (VOR) in response to impulsive head rotations in horizontal and vertical planes; and (6) vergence. We characterized the direction and intensity of nystagmus in central and eccentric gaze, as the subject wore illuminated Frenzel goggles in a completely dark room, under the following conditions: (1) head erect and stationary; (2) after vigorous horizontal or vertical head-shaking for 10 seconds; (3) after hyperventilating for 20 seconds; (4) during Dix-Hallpike positional testing, with either the right or left ear dependent; (5) in a central "head-hanging" position (lying supine with neck extended about 45 degrees); (6) lying supine on a flat couch; (7) lying on one side or the other on a flat couch; (8) with the head prone (sitting, bent forward at the waist). Although some normal subjects (i.e., individual who lack any clear history of vestibular disturbance) may show minor degrees of nystagmus during some of these tests [4, 9], we were interested in detecting common and consistent abnormalities on bedside vestibular examination in our genetically diagnosed group of SCA6 patients.

Results

Sixty-two percent of patients (13/21) reported attacks of vertigo, which were usually brief (seconds to minutes, occasionally hours) and recurrent. Attacks of vertigo preceded the development of ataxia in 12/13 patients (mean duration of vertigo prior to the ataxia = 6.8 years, SD = 3.6, maximum = 10 years). Vertigo was induced by a change of head position in 10/13 patients, most commonly during standing and looking up (neck extension). Exercise appeared to precipitate attacks in 5 individuals. Pre-syncopal symptoms were uncommon and orthostatic hypotension was absent in all patients. Furthermore, phobic forms of dizziness were uncommon and migraine occurred in only 14 % of our study cohort. Auditory symptoms were rare and hearing tests were normal in 79 % of our patients.

Best corrected visual acuity was 20/30 (6/9 equivalent) or better in at least one eye in 16/21 patients; it deteriorated during head shaking in 6/21. Stereopsis was absent in 12/21 patients, with the other 9 patients having reduced stereoacuity, based on published, age-adjusted normative ranges [10] (Table 1).

The main findings of the vestibular examination are summarized in Table 2. Ocular alignment was normal except for one patient with a skew deviation. Convergence was impaired in two patients, and absent in 1 patient (H, Table 1), with poor vision down to counting fingers due to bilateral cataracts and age-related macular degeneration. Fixation was disrupted by horizontal saccadic intrusions (square-wave jerks) in 6 patients. Saccades were initiated promptly with normal speed; 1 patient showed hypometria and 6 hypermetria. Ocular and eye-head pursuit was saccadic in 17/21 patients. The VOR showed abnormalities in 4 patients, being hypoactive in 1 (corrective saccades opposite to direction of head turn), and with corrective downward saccades in 3 (head rotation induced upward slow phase of downbeat nystagmus).

Examination for nystagmus (Frenzel goggles) with the head erect revealed 8 patients with downbeat nystagmus, and 8 with horizontal gaze-evoked nystagmus. The combination of downbeat and horizontal nystagmus on eccentric gaze produced nystagmus with down-and-out quick phases ("side-pocket" nystagmus) in 9 patients. Head-shaking induced nystagmus in 14 patients; 10 developed downbeat nystagmus with this manoeuvre. Hyperventilating 20 deep breaths did not induce nystagmus in patients who showed none previously, although it did increase existing nystagmus in some patients. The Dix-Hallpike manoeuvre induced mixed upbeat-torsional nystagmus lasting about 10 seconds (with attendant vertigo), typical of benign paroxysmal positional vertigo (BPPV) of the posterior canal variant [4], in only one patient. When patients were placed in a central head-hanging position, downbeat nystagmus in central gaze tended to increase in intensity and appeared for the first time in four patients (total of 11); side-pocket nystagmus was present in 13. When patients lay supine, side-pocket nystagmus developed in 15 patients. When patients lay flat and turned onto their right or left side, apogeotropic nystagmus (beating away from the ground) developed in 9 of them, unaccompanied by vertigo. With the head positioned prone, downbeat nystagmus in central gaze was present in 10 patients and side-pocket

Table 1 Visual parameters in our SCA6 cohort

Patient	Gender	Age/yrs	Snellen Visual Acuity			Stereopsis/″
			Right (20/)	Left (20/)	Head Shaking	
A	Female	54	25	30	Same	100
B	Female	70	25	25	Same	100
C	Female	66	30	70	Worse	100
D	Female	53	25	25	Same	0
E	Male	62	30	30	Same	200
F	Female	60	25	20	Worse	0
G	Female	80	200	200	Same	0
H	Female	85	CF	CF	Same	0
I	Male	72	20	20	Worse	0
J	Male	75	30	40	Same	0
K	Female	64	30	30	Same	100
L	Female	59	70	70	Same	0
M	Female	61	25	25	Same	100
N	Male	74	25	30	Worse	0
O	Female	63	50	50	Same	0
P	Female	77	100	200	Worse	0
Q	Female	69	20	30	Worse	0
R	Male	47	25	30	Same	100
S	Male	66	20	20	Same	100
T	Male	72	30	30	Same	400
U	Female	79	30	800	Same	0

CF counting fingers; *yrs* years; ″ = seconds of arc

Table 2 Summary of main findings on vestibular examination

	Findings (Number/Percentage)
Ocular Motor Testing*	
Fixation	Horizontal square-wave jerks (6/29 %)
Saccades	Hypometria (10/48 %) Hypermetria (6/29 %)
Smooth pursuit	Saccadic pursuit (17/81 %)
VOR	Hypoactive (1/5 %) Induced downbeat (3/14 %)
Vergence	Impaired (2/10 %) Absent due to poor vision (1/5 %)
Nystagmus (Frenzel goggles)	
Head erect	Downbeat (8/38 %) Horizontal gaze-evoked (8/38 %) Side-pocket** (9/43 %)
After head-shaking	Same plane (3/14 %) Orthogonal to head-shaking (11/52 %)
Central, head-hanging	Downbeat (11/52 %) Side-pocket** (13/62 %)
Supine	Downbeat (10/48 %) Side-pocket** (15/71 %)
Lying on right or left side	Apogeotropic – beating away from ground (9/43 %)
Prone	Downbeat (10/48 %) Side-pocket** (11/52 %)

* Ocular alignment was normal in all patients except for one with skew deviation;
** Nystagmus beating diagonally down, with the eyes in eccentric horizontal gaze

nystagmus in 11. When the results of all testing were combined, only 1/21 patients showed no nystagmus during any test condition.

Discussion

Our main findings were that attacks of vertigo occurred in most of our patients with SCA6, often pre-dating the development of ataxia, and that almost all patients showed findings indicating central (not peripheral) abnormalities during systematic bedside vestibular testing. These findings raise several questions. First, how do patients with SCA6 differ from other patients who present with recurrent episodes of vertigo? Second, what do the abnormalities on the examination tell us about the nature of the vestibular disorder in SCA6? Third, how do our present findings relate to previous studies of SCA6 and episodic ataxia type 2 (EA2), which are both due to mutations in *CACNL1A4*?

The attacks of vertigo in our SCA6 patients were usually brief, lasting seconds or minutes, and typically recurred several times per year. Rarely, attacks lasted hours or days. Head movements, especially extension of the neck, often precipitated attacks. This history might raise the possible diagnosis of BPPV. However, other common causes of vertigo, such as ear disease, migraine, or pho-

bic positional vertigo were less likely to be suggested by our patient's symptomatology. Careful examination supported the diagnosis in almost all of our patients, notably by the forms of nystagmus observed behind Frenzel goggles. Thus, downbeat nystagmus, horizontal gaze-evoked nystagmus, and their combined form (side-pocket nystagmus) were common findings, provided head shaking and comprehensive positional testing was performed. Interestingly, the supine position induced the highest incidence of nystagmus. Only one of our patients showed symptoms and signs supportive of a diagnosis of posterior canal BBPV. Furthermore, most patients showed other ocular motor abnormalities, such as impaired smooth pursuit and dysmetric saccades. Intriguingly, the vertigo resolved in 4/13 subjects before the onset of the ataxia. This implicates ion channel dysfunction in the pathophysiology of these transient symptoms, rather than neuronal loss. In addition, a history of paroxysmal vertigo preceding the ataxia may be a useful feature discriminating SCA6 from other late-onset ataxic disorders, prompting appropriate molecular genetic testing.

The predominant effect of changes of head posture in inducing central forms of nystagmus suggests that, in SCA6, cerebellar control of vestibular mechanisms is impaired. First, during head rotations (impulsive stimuli or head shaking) downbeat nystagmus was often induced; this implies a directional abnormality of the angular VOR [11]. Second, sustained nystagmus on adopting specific head positions implies abnormal control of otolithic inputs; for example, downbeat nystagmus appearing in a central "head-hanging" position. An unexpected finding was apogeotropic nystagmus (beating away from the ground) when patient lay on one side or the other. Although this form of nystagmus is encountered in the lateral-canal form of BPPV [4], absence of vertigo and associated abnormalities in our patients distinguished them from disease of the vestibular labyrinth. The pathogenesis of apogeotropic nystagmus in our patient may be similar to one mechanism proposed for downbeat nystagmus [12], which suggests abnormal cerebellar control of otolith-ocular responses. However, another proposal concerns a mechanism that normally adjusts for the eccentric mass of the eye, which may depend on cerebellar governance [13].

Another unexpected finding was that stereopsis was abnormal in our whole study cohort; being completely absent in 57 % of patients and sub-normal in the remaining group, even after adjusting for age-related decline in stereoacuity. In 4/21 patients, the complete loss of stereopsis could be ascribed to poor vision in one or both eyes, but stereoacuity is not significantly affected until visual acuity drops to 20/100 or worse [14]. The latter therefore cannot be the explanation for the remaining 17 patients, who had visual acuities > 20/100 in both eyes, in addition to intact binocular vision and convergence. This finding deserves further study given recent evidence implicating the cerebellum in the processing of visual information relating to depth perception [15].

Finally, how did our patients compare with those with EA2, both of which affect the same calcium channel gene: *CACNL1A4* [16–18]? Exercise worsened attacks in five of our SCA6 patients, but the typical history of exercise-induced vertigo, ataxia and dysarthria, sometimes with headache, was not reported. Furthermore, our SCA6 patients' attacks of vertigo were shorter than those of EA2, which usually last hours to days [18], although some overlap of symptomatology is reported [19]. Improvement of symptoms with acetazolamide, which is common with EA2 [18], was noted in only two of our patients. A formal, comprehensive comparison of the vestibular examination in SCA6 and EA2 might identify clinical signs that help distinguish these two phenotypes as well as give clues to the difference in pathogenesis. Such a study would be strengthened by the measurement of eye and head movements, application of experimental tests of specific pathogenic mechanisms (e.g., the several hypotheses proposed to account for downbeat nystagmus [20]), and comparison with a group of control subjects, who may occasionally show minor degrees of nystagmus during positional testing or following head shaking.

Conflict of interest The authors declare no conflict of interest.

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