Vertigo and vestibular abnormalities in spinocerebellar ataxia type 6

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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 of vertigo.

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
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 migraine 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...