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Cerebellar ataxia with bilateral vestibulopathy: description of a syndrome and its characteristic clinical sign

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Summary

We report four patients with the syndrome of cerebellar ataxia with bilateral vestibulopathy (CABV) and, using search coil oculography, we validate its characteristic clinical sign, namely impairment of the visually enhanced vestibulo-ocular reflex (VVOR) or doll's head reflex. In our four patients, CABV began in the sixth decade of life; they are still ambulant and self-caring 8–20 years after onset. The cause of CABV in our four patients is unknown. None has a family history of cerebellar or vestibular disease; spinocerebellar ataxia (SCA) 1, 2, 3, 6, 7 and Friedreich's ataxia were excluded by genetic testing. Three of the four have a sensory peripheral neuropathy but none has extrapyramidal or significant autonomic problems, and none has gluten sensitivity. We measured eye rotations in response to head-on-trunk head rotations and in response to head-and-trunk (*en bloc*) rotations. Horizontal smooth pursuit (SP), vestibulo-ocular reflex (VOR) and VVOR gains were measured in response to head rotations at 0.1, 0.3, 0.6 and 1.0 Hz. The optokinetic reflex (OKR) was tested by measuring optokinetic nystagmus slow phase velocity during constant 50°/s rotation of the subject in light. The results showed that CABV patients had impairment of all three compensatory eye movement reflexes, the VOR, the OKR and SP. During VVOR testing, as the frequency of head rotation increased from 0.1 to 1.0 Hz, eye velocity failed to match head velocity, gaze velocity increased, and gaze position errors developed, which were corrected with bursts of saccades, the basis of the clinical sign of an impaired VVOR.

Keywords: cerebellar ataxia; bilateral vestibulopathy; clinical test; vestibulo-ocular reflex; smooth pursuit; optokinetic

Abbreviations: BV = bilateral vestibulopathy; CA = cerebellar ataxia; CABV = cerebellar ataxia with bilateral vestibulopathy; MSA = multiple system atrophy; OKR = optokinetic reflex; SCA = spinocerebellar ataxia; SP = smooth pursuit; VOR = vestibulo-ocular reflex; VORS = visually suppressed vestibulo-ocular reflex; VVOR = visually enhanced vestibulo-ocular reflex

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Introduction

During natural activities such as walking or running, gaze is stabilized by a combination of visual and vestibular reflexes (Grossman *et al*., 1989), known as the visually enhanced vestibulo-ocular reflex (VVOR). The contribution of visual reflexes is most obvious during low-frequency, predictable head rotations. For example, if a normal subject views a small target which oscillates from side to side, smooth pursuit (SP) and perhaps a separate fixation system (Leigh *et al*., 1994) will produce smooth compensatory eye movements that accurately track the target up to a frequency of ~1 Hz and a velocity of ~100°/s (Meyer *et al*., 1985). Similarly, if the subject views a whole scene that oscillates from side to side, the optokinetic reflex (OKR) will produce smooth compensatory eye movements in a similar dynamic range to SP. In contrast, when the subject oscillates their head from side to side in the dark, the vestibulo-ocular reflex (VOR) will produce smooth compensatory eye movements at frequencies from <0.1 to >6 Hz. In this situation, the gain of the VOR, defined as instantaneous eye velocity divided by instantaneous head velocity, depends on frequency and rises from ~0.6 at 0.1 Hz to nearly 1.0 at 0.5 Hz and above (Gauthier *et al*., 1984; Grossman *et al*., 1989; O'Leary and Davis, 1990;

Peterka *et al*., 1990; Della Santina *et al*., 2002). If the subject now oscillates their head while viewing a target or a scene, the combination of SP, optokinetic, fixation and vestibulo-ocular reflexes, i.e. the VVOR, will produce near-perfect smooth compensatory eye movements. The VVOR gain is close to 1.0, from <0.1 to >6 Hz, thus maintaining retinal slip velocity below 3–5°/s, the level at which vision starts to degrade (Grossman *et al*., 1989; Demer, 1996; Tian *et al*., 2002).

In patients with most types of genetically identified hereditary spinocerebellar ataxia (SCA), SP and OKR gains are low, but VOR gain is low only in those with SCA1 or SCA3 (Büttner *et al*., 1998; Bürk *et al*., 1999). In contrast, patients with bilateral vestibulopathy (BV) have normal SP and OKR gains, but have, by definition, low VOR gain (Yee *et al*., 1978; Zasorin *et al*., 1983). However, patients with impaired SP and OKR, usually due to cerebellar ataxia (CA), produce a near-normal VVOR using their VOR. Similarly, patients with BV produce a near-normal VVOR below ~1 Hz using their SP and OKR (Baloh *et al*., 1981). Impairment of the VVOR below ~1 Hz therefore indicates double pathology, involving both vestibular and cerebellar pathways.

Here we report four patients with low VVOR gain, none of whom had SCA1 or SCA3, or a family history of cerebellar or vestibular disease. However, we could not rule out the olivopontocerebellar form of multiple system atrophy (MSA). Each presented with progressive gait ataxia and could not stabilize gaze during slow (<1 Hz) head oscillations. Each patient had easily observable compensatory saccades while trying to view an earth-fixed target during horizontal or vertical head oscillation. This phenomenon, known as an absent 'doll's head reflex', was first reported by Bronstein *et al*. (1991) in two patients thought to have MSA, and then by Waterston *et al*. (1992) in one. In our four patients, we studied SP and the OKR, as well as the VOR and the VVOR with both head-on-trunk and head-and-trunk rotations. The aim of the study was to describe in detail this clinical syndrome of cerebellar ataxia with bilateral vestibulopathy (CABV) which was first reported by Bronstein *et al*. (1991) and to analyse and validate its characteristic clinical sign: impairment of the VVOR.

Methods

Head-on-trunk rotations

Experimental protocol and recording system

Each patient sat comfortably with the head at the centre of a $2 \times 2 \times 2$ m wooden frame that incorporated magnetic field coils (CNC Engineering, Seattle, WA). Head and right eye positions were recorded with pre-calibrated dual scleral search coils (Skalar, Delft, The Netherlands); head and eye coil voltage signals were low-pass filtered to 100 Hz and digitally recorded to a PC at a 1000 Hz sample rate. Full details of the recording method have been published (Aw *et al*., 1996). The first set of experiments with each patient was with the head fixed in a head holder; we tested for spontaneous and gaze-evoked nystagmus, measured Listing's plane and recorded SP. The second set of experiments involved passive head oscillations in which one of us standing behind the patient smoothly turned, by hand, the patient's head from side to side. The patient kept trying to look at either: (i) an earth-fixed visual target at 94 cm in the otherwise darkened laboratory for VVOR testing; (ii) the remembered position of the same target, after it was turned off and the room was totally dark for VOR testing; or (iii) a miniature light-emitting diode (LED) 32 cm directly in front of the right eye and rigidly attached to a headband for visually suppressed VOR (VORS) testing. In the third set of experiments, the patient's head was quickly turned to one side or the other for the head impulse test (for details see Aw *et al*., 1996; Cremer *et al*., 1998).

Gaze-evoked nystagmus

The patient's head was secured in a wooden holder. In the otherwise dark room, patients fixated a laser spot at 94 cm directly in front of the right eye. When the laser spot disappeared, patients were asked to continue looking at the remembered position of the laser spot. The computer-controlled laser spot initially was positioned directly in front of the right eye for 10 s; after this time, the laser was switched off for 10 s and then switched on for a further 10 s. This sequence was repeated for different laser spot positions: straight ahead, left 10°, left 30°, right 10°, right 30°, up 20° and down 20°. Eye position was recorded so that gaze-evoked nystagmus could be measured with and without fixation.

Saccade velocity and Listing's plane

The patient made a series of voluntary saccades to a set of 24 targets displayed on a screen at 94 cm. Saccades were manually identified. Saccades that did not have the typical bell-shaped velocity profile, e.g. when a second saccade commenced before the first was completed, were excluded from the analysis. The duration of a saccade was defined as the period of time in which eye velocity was >5°/s. The amplitude of the saccade was defined as the change in eye position during the saccade, and saccade velocity was defined as the peak eye velocity during the saccade. We measured 10–15 horizontal and 10–15 vertical saccades for each subject and fit the data to quadratic equations to obtain a main sequence (Bahill *et al*., 1975). Listing's plane was calculated from the eye positions (Haslwanter, 1995; Migliaccio and Todd, 1999).

Head impulses

Passive, unpredictable 15–30°, 150–350°/s and 1500–3500°/s^2 horizontal head impulses were delivered manually by an experimenter. The patient was asked to keep looking at the laser spot while a head impulse was delivered. Each patient received horizontal head impulses, eight to the left and eight to the right in random sequence.

VORs

A plastic plumb-bob was attached to the frame above the patient: the point at which the plumb-bob projected onto the top of the head was marked and served as a reference position after the wooden head holder was removed. For the VVOR test, the patient tried to fixate on a laser spot directly in front of the right eye while an experimenter smoothly oscillated the patient's head from side to side about ±10° to the beat of a computer-controlled metronome. The metronome was set to beat at four different low frequencies, 0.1, 0.3, 0.6 and 1.0 Hz. This resulted in respective peak head velocities of ~6, 19, 38

and 63°/s. At each metronome frequency, 30 s of data was recorded. For the VOR test, all the head oscillations were repeated while the patient tried to fix the remembered position of the laser spot after it had been turned off and the room was totally dark. For the VORS test, the patient tried to fixate a miniature LED at the end of a 32 cm arm directly in front of the right eye rigidly attached to a headband.

SP

Each patient was asked to fix and then track a laser spot moving horizontally, sinusoidally at four different frequencies, 0.1, 0.3, 0.6 and 1.0 Hz, with amplitude ±10°, and with peak target velocities of 6, 19, 38 and 63°/s. At each frequency, 30 s of data was recorded.

Head-and-trunk (en bloc) rotations

The patients were seated on a rotating chair driven directly by a 220 Nm servo-motor, controlled by an analogue velocity signal from a PC. The walls of the cabin surrounding the chair were black with regularly spaced white vertical stripes subtending a visual angle of 40° upwards and 50° downwards. The head was secured over the earth-vertical central axis of the chair by a head holder. The horizontal position of the right eye was measured by infrared oculography, with the angular position and velocity signals being digitally recorded by the PC at a 200 Hz sample rate. This is our standard laboratory system used for daily clinical testing with a horizontal linear range of at least ±20°.

Gaze-evoked nystagmus was sought with and without fixation at 15° left and right. For the VVOR and VOR measurement, the patient was rotated sinusoidally at two different frequencies: 0.1 and 0.33 Hz a constant amplitude of 50°/s with respective position amplitudes of about ±80 and ±24°. For VVOR testing, the cabin was lit so that the patient could see the stripes while being oscillated from side to side; for VOR testing, the cabin was totally dark; for VORS testing, the patient tried to fixate a miniature LED attached to the chair frame 64 cm in front of the interpupillary point. For OKR testing, the cabin was lit and the chair was rotated at a constant 50°/s for 60 s.

Data analysis

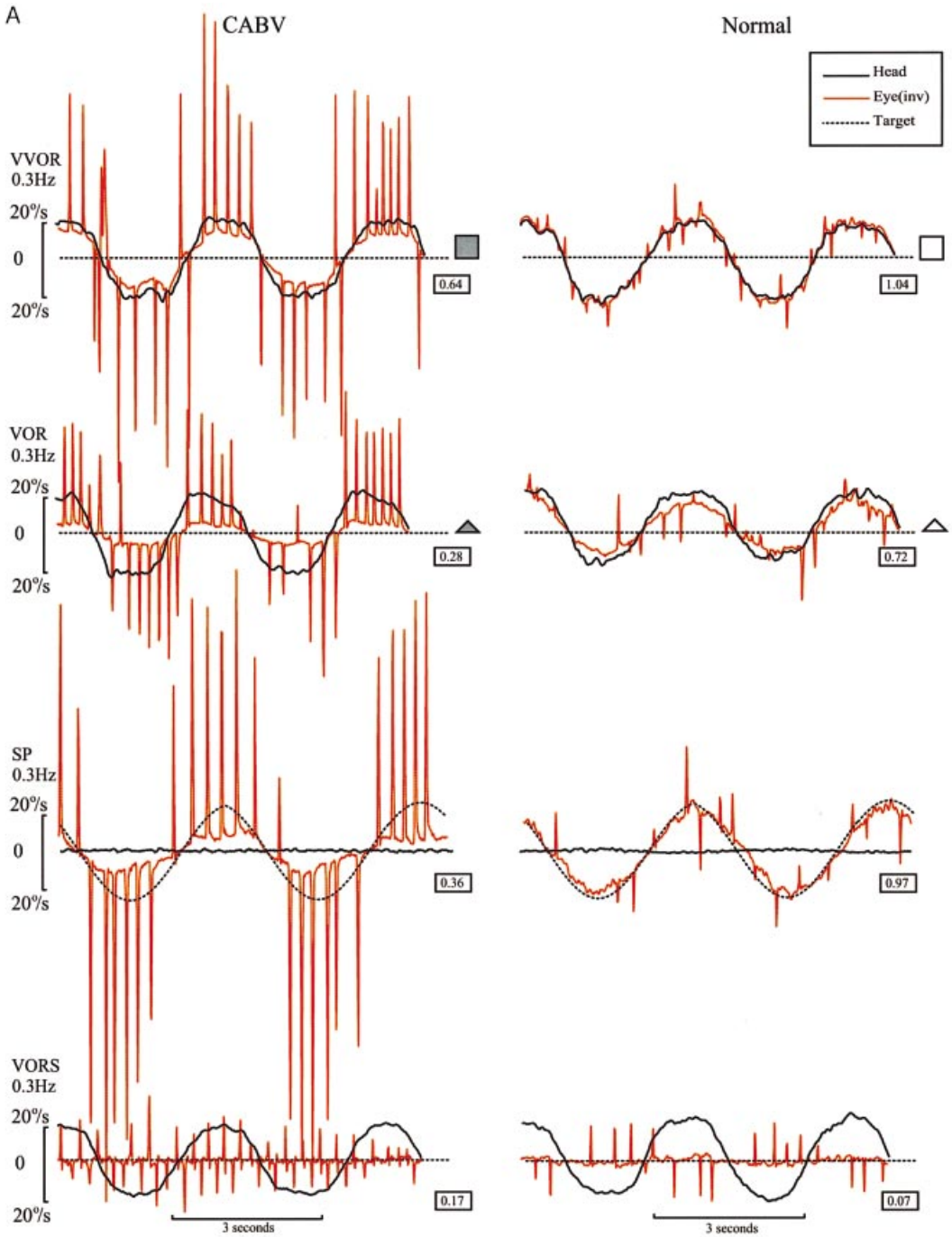
For head-on-trunk rotations, data contaminated with blinks, search-coil slippage or other artefacts were discarded. Saccades were identified visually and culled manually for analysis of peak amplitude and velocity. The SP gain was calculated by dividing the average peak eye-in-space velocity by peak target velocity. The VVOR, VOR and VORS gain was calculated by dividing the average peak eye-in-head velocity (peaks in the sinusoidal velocity trace) by the average head velocity (at peak eye-in-head velocity). The number of compensatory saccades per second (saccade frequency) was calculated by counting the total number of saccades in each 30 s data recording and dividing by 30. The average amplitude and peak velocity of saccades were calculated for each 30 s data recording. For head-and-trunk rotations, the saccades were manually cut from the horizontal eye velocity trace and were not included in the analysis. The VOR and VVOR gain was calculated by dividing the average peak eye-in-head velocity (peaks in the sinusoidal velocity trace) by the average chair velocity (at peak eye-in-head velocity). The OKR gain was calculated after 30 s of constant velocity rotation so that the contribution from SP to slow phase eye velocity was minimal.

Written informed consent was obtained from all subjects and patients prior to testing, according to the Declaration of Helsinki. The experimental protocol was approved by the Human Ethics Committee of the Central Sydney Area Health Service.

Patients and subjects

The CABV patients were identified in our Balance Disorders Clinic by finding the characteristic sign on clinical examination: impairment of the VVOR, i.e. of the doll's head reflex (Bronstein, 2003). This abnormality is due to combined impairment of VOR and SP as indicated by bursts of compensatory saccades when the patient's head was slowly and smoothly oscillated from side to side while fixating an earth-fixed target straight ahead. There were two women and two men; each presented between 50 and 60 years of age with slowly increasing gait ataxia and later developed dysarthria. All had problems standing: the Romberg test was positive in all four, initially only while standing on a foam mat (Weber and Cass, 1993) but later even when standing directly on the floor. Limb ataxia was less obvious than gait ataxia. Only one patient developed gaze-evoked horizontal nystagmus; another developed gaze-evoked oblique downbeating nystagmus as well as rebound nystagmus (Bronstein *et al*., 1987). All had, by definition, bi-directionally impaired horizontal and vertical VVOR as well as bi-directionally impaired horizontal and vertical SP and impulsive VOR, but normal VOR suppression. Three had clinical and electrophysiological evidence of a sensory peripheral neuropathy; one patient had presented with this, and his sural nerve biopsy showed a severe axonal neuropathy. One presented with BV and only developed cerebellar signs ~4 years later. Despite the severe BV, none of our patients, just as neither of the patients previously reported by Bronstein *et al*. (1991), complained of, or even admitted to, the characteristic symptom of BV, oscillopsia during natural activities (Rinne *et al*., 1998). None had extrapyramidal features such as bradykinesia, tremor or rigidity. Only one patient had symptoms suggesting autonomic involvement (impotence) and none had postural hypotension not attributable to medication. None had a hearing loss not attributable to age and noise. None had abused alcohol and none had been treated with aminoglycosides (Halmagyi *et al*., 1994). On MRI, all showed cerebellar atrophy but not brainstem atrophy and no relevant white matter hyperintensities. One patient had an incidental small intracanalicular acoustic neuroma that has not changed in size over 3 years observation. None of the patients had a family history of progressive ataxia, and at least two first-degree relatives of each patient were clinically examined by one of the authors (G.M.H.). Genetic tests for SCA1, 2, 3, 6, 7 and for Friedreich's ataxia were negative in all four patients, as were serological tests for coeliac disease (Bürk *et al*., 2001; Hadjivassiliou *et al*., 2003). All four are still alive and still independent 8–20 years after onset of symptoms.

For head-on-trunk rotation testing, in addition to the four CABV patients, we studied one patient with only CA, one patient with only BV and four normal subjects (range 25–52 years). The CA patient (53 years) had a 2-year history of increasing gait ataxia. On examination, there was bi-directional horizontal gaze-evoked oblique downbeating nystagmus, bi-directional impairment of horizontal and vertical SP and VORS. The horizontal and vertical VOR was normal on impulsive testing. When trying to maintain visual fixation while slowly turning his head from side to side, he



responded normally with smooth compensatory eye rotations; in other words, the VVOR was normal. Brain CT showed no cerebellar atrophy; caloric tests of lateral semicircular canal function and an audiogram were normal. DNA tests for SCA1, SCA2, SCA3 and SCA6 were negative. The diagnosis was idiopathic progressive CA (Abele *et al*., 2002). The BV patient (48 years) presented with sudden onset of imbalance without any vertigo, hearing loss and no history of aminoglycoside exposure. He admitted to experiencing vertical oscillopsia during running. On clinical examination, he had a severe bi-directional impairment of the horizontal and vertical VOR on impulsive testing and a positive Romberg test, but only when standing on a foam mat. There was no other abnormality, in particular no abnormality of SP eye movements, no gait or limb ataxia and no dysarthria. When trying to maintain visual fixation while slowly turning his head from side to side, he responded normally with smooth compensatory eye rotations; in other words,

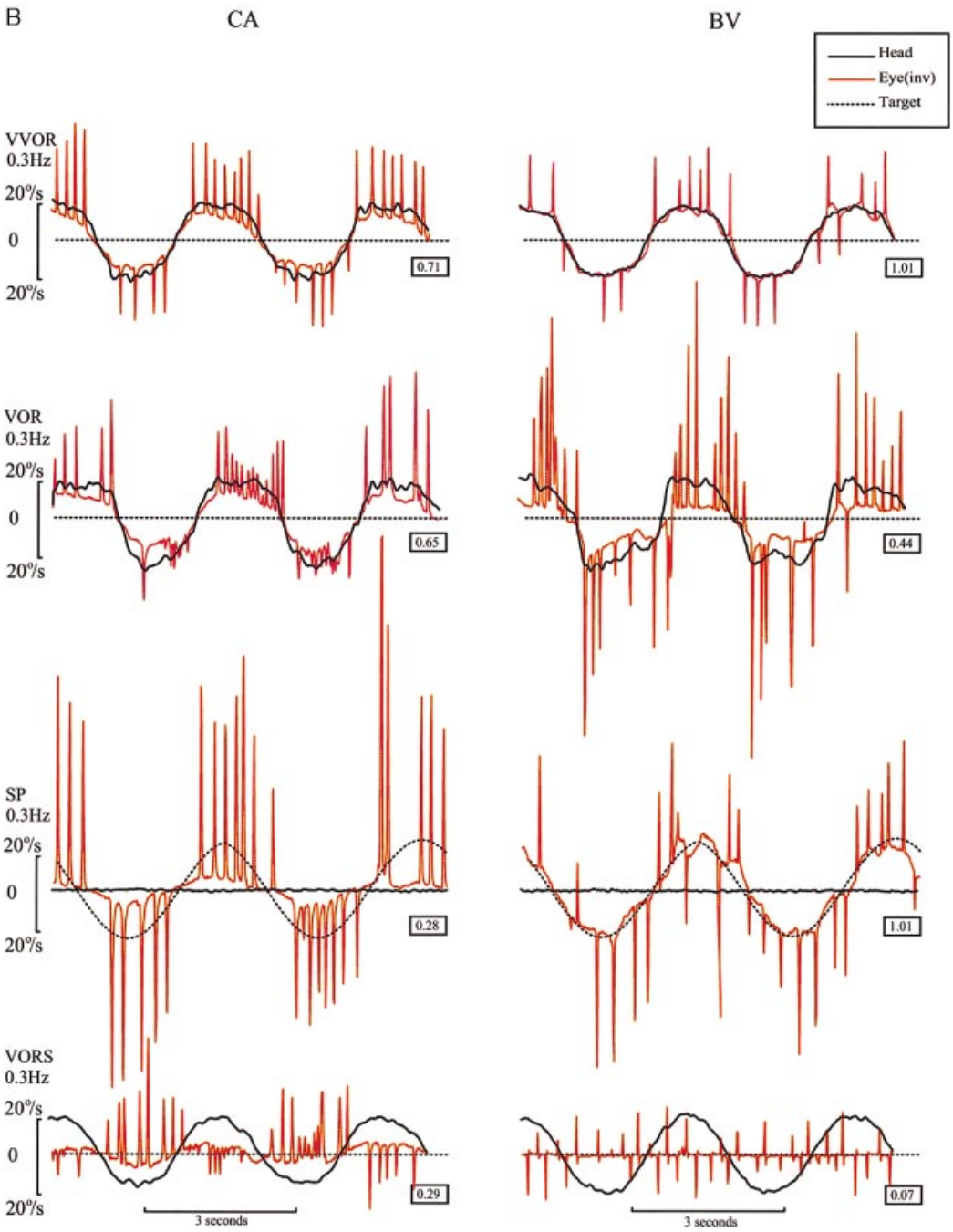


Fig. 1 Testing the horizontal VVOR, VOR and VORS with head-on-trunk rotations and horizontal SP, all at 0.3 Hz. (**A**) Results from a CABV patient and a normal subject. (**B**) Results from a pure CA patient and a BV patient. Head velocity (bold), inverted eye velocity (red) and target velocity (dashed) are shown. The key feature to note in each of the 16 panels is the size and frequency of the compensatory or catch-up saccades, as an index of the gaze error that accumulates during attempted fixation of a real earth-fixed target during VVOR testing of an imagined earth-fixed target during VOR testing, of a head-fixed target during VORS testing or of a moving target during SP testing. The lower the gain of the compensatory slow eye movements (gain shown in a box for each condition), the higher the frequency and magnitude of the compensatory saccades. During VVOR testing, the CABV patient makes more and larger compensatory saccades than either the CA or the BV patient; in contrast, the normal subject hardly makes any. These saccades are observable clinically and constitute the characteristic clinical sign of CABV: bursts of corrective saccades as the patient views an earth-fixed target while turning the head from side to side. In the CABV and BV patients VORS looks almost normal (low gain) and there are few saccades since there is little or no VOR to suppress. In contrast, VORS is abnormal in the CA patient, with gain of 0.29 (normal <0.2). The open and filled triangle and square identify data that are also shown in Fig. 2 and, desaccaded, in Fig. 3.

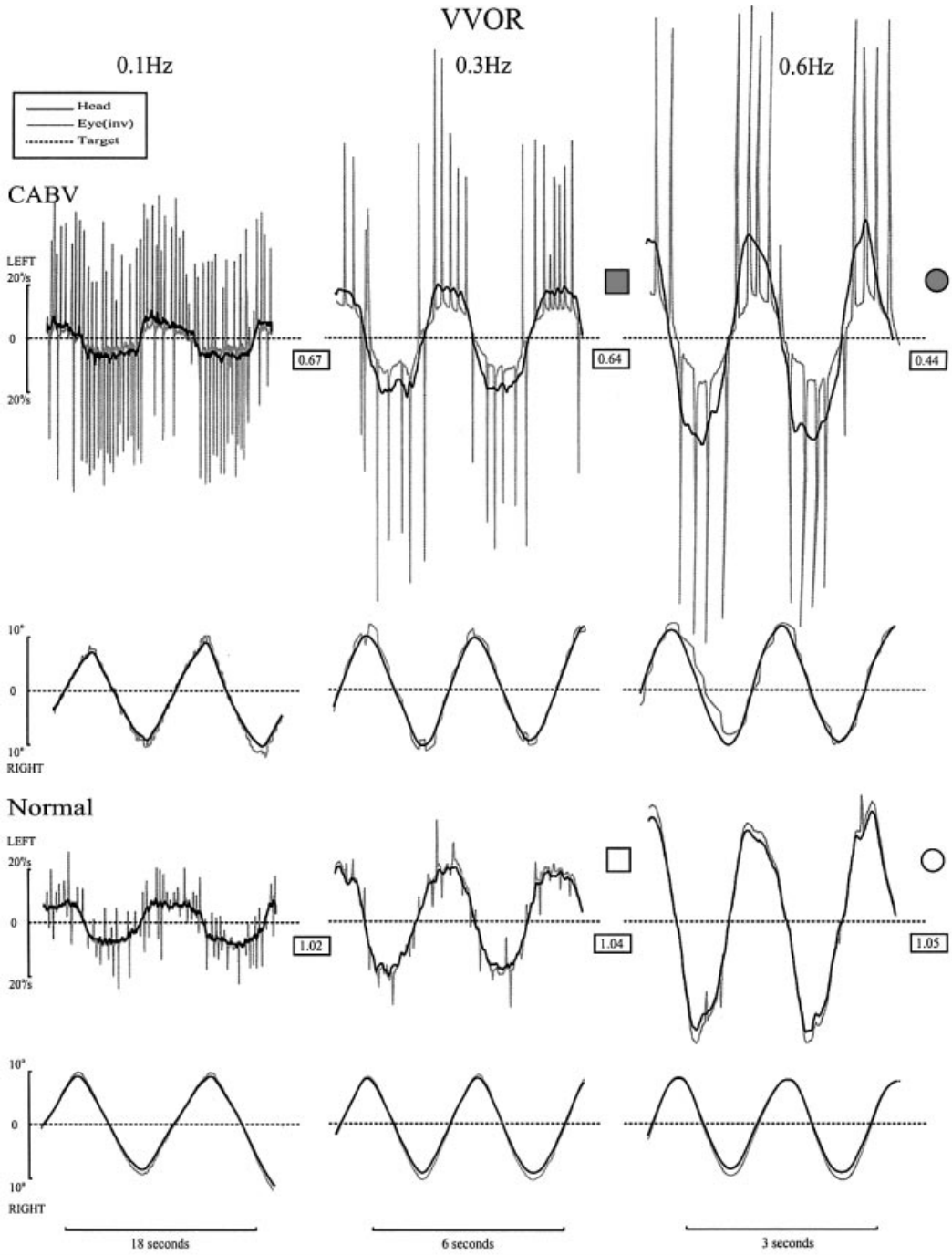


Fig. 2 The horizontal VVOR in a CABV patient and in a normal subject, during head-on-trunk rotation at increasing frequency and velocity. In the CABV patient, unlike in the normal subject, VVOR gain decreases with increasing head rotation frequency and velocity, with larger more obvious compensatory saccades. The corrective saccade amplitudes are shown in the position traces and typically ranged 0.5-6 degrees. This is shown graphically for each of the four CABV patients in Figs 4 and 5. The open and filled square and circle identify data that are also shown in Fig. 1 and, desaccaded, in Fig. 3.

his VVOR was normal. Caloric testing at 0°C and rotational chair testing at 100°/s^2 showed no nystagmus responses. Audiogram and brain MRI were normal. The diagnosis was idiopathic BV (Rinne *et al*., 1998).

For head-and-trunk (rotational chair) testing, we compared the results of the four CABV patients with the normative database we use for routine clinical testing.

Results

Head-on-trunk rotations

Gaze-evoked nystagmus

Fixating 10° to the left or right, no patient had a gaze-evoked nystagmus that had a slow-phase velocity >1°/s. Fixating 30° to the left or right, all four CABV patients

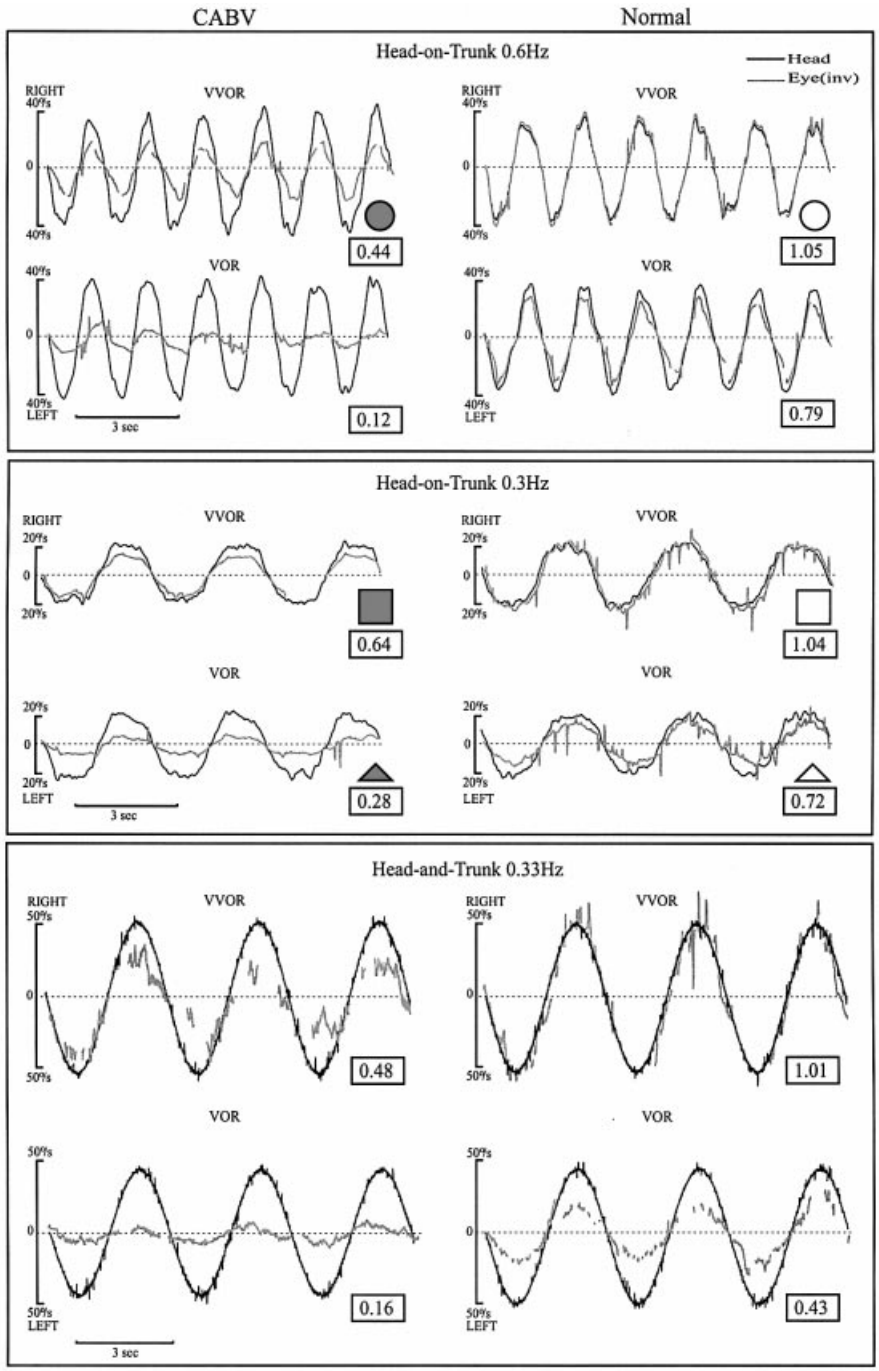


Fig. 3 The horizontal VVOR and VOR during head-on-trunk testing at 0.6 Hz (top) and at 0.3 Hz (middle) compared with head-and-trunk (*en bloc*) testing in a rotating chair at 0.33 Hz (bottom). Head velocity is shown in black, and desaccaded inverted eye velocity in grey. The results from a CABV patient are shown on the left and results from a normal subject on the right. Note that peak head velocity is set to 50°/s with head-and-trunk rotation, but with head-on-trunk rotation it is only 20°/s at 0.3 Hz and 40°/s at 0.6 Hz. The VVOR gain in the normal subject is close to 1.0 during both head-on-trunk and head-and-trunk testing, whereas in the CABV patient the VVOR gain is only 0.48 during 0.33 Hz head-and-trunk testing and 0.64 at 0.3 Hz head-on-trunk testing. The open and filled circle, triangle and square identify data that are also shown in Figs 1 and 2, shown here desaccaded.

and the CA patient had a gaze-evoked nystagmus with a downbeat component and a horizontal slow-phase velocity from 3.4 to 9.6°/s.

Saccade velocity

Peak saccade velocities calculated from the voluntary saccades made during the measurement of Listing's plane were all

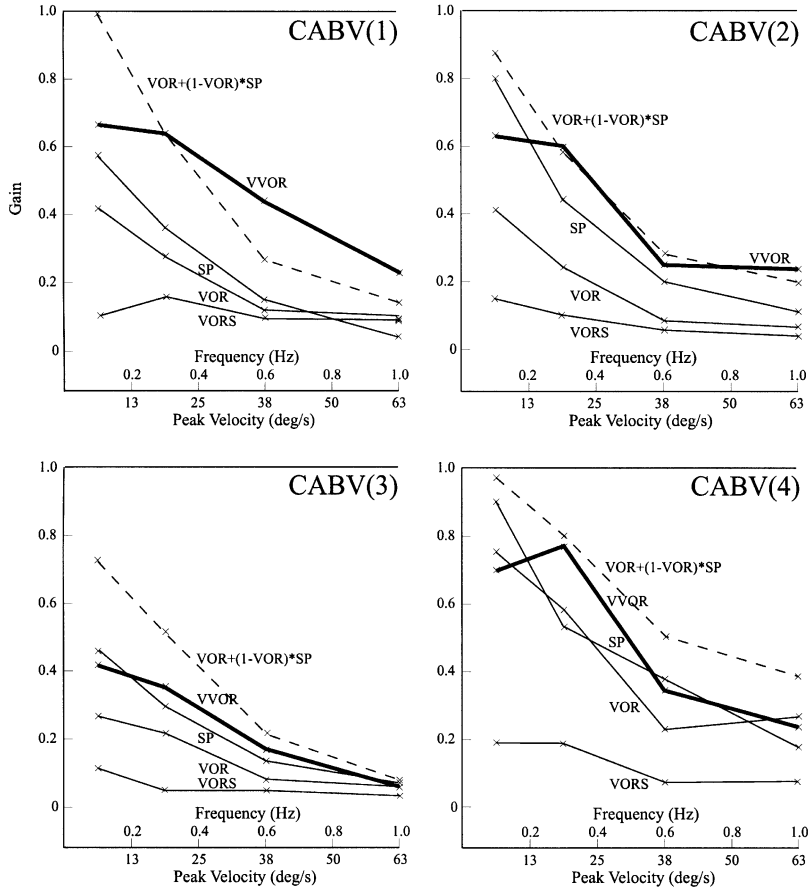


Fig. 4 The gains of the horizontal VVOR, VORS and VOR as a function of the frequency and velocity of head rotation during head-on-trunk testing, and the gain of SP as a function of target frequency and velocity in each of the four CABV patients. Note that although there are large variations between patients in each of the three measures at the lowest stimulus frequency (0.1 Hz), at the highest stimulus frequency (1.0 Hz) all four patients on all three measures have gains of <0.3. VVOR gain is the measure which most clearly distinguishes CABV patients from normals, since VVOR gain is normally 1.0 or even a little higher at 1.0 Hz. Dashed lines show VVOR gain from the equation [VVORgain = VORgain + (1 – VORgain) × SPgain] which makes a good approximation of the actual data from CABV patients 2 and 3 and a fair approximation in patients 1 and 4.

within the main sequence for horizontal saccadic eye movements. Vertical, mainly upward, saccade velocity was just below normal in one CABV patient aged 76, probably because of ageing rather than because of the neurological disease.

Listing's plane

The thickness of Listing's plane for all patients (CABV, CA and BV) was similar to that of normal subjects, indicating that the torsional eye position constraints imposed by Listing's Law during saccades still held. The orientation of Listing's plane in CABV patients and the CA patient was not the same as that of the BV patient and that of normal subjects. Listing's plane in the CABV and CA patients was rotated laterally in the temporal direction on average by ~5°, whereas in the BV patient and in normal subjects it was rotated temporally by ~1°.

Head impulses

Normal subjects had an impulsive VOR gain of 0.98 ± 0.03, a result similar to that previously reported (Aw *et al*., 1996; Cremer *et al*., 1998). In contrast, the VOR gain in CABV patients was only 0.10 ± 0.04 and in the BV patient it was only 0.07 ± 0.02.

VOR

The VOR gains of CABV patients and of the BV patient were lower than those of normal subjects and, unlike in normal subjects, decreased rather than increased with increasing stimulus frequency (Figs 2, 4 and 5). In normal subjects, the mean VOR gain was 0.62 ± 0.06 at 0.1 Hz, increasing to 0.77 ± 0.04 at 1 Hz. In the CABV patients, the mean VOR gain was 0.47 ± 0.20 at 0.1 Hz, decreasing to 0.12 ± 0.09 at

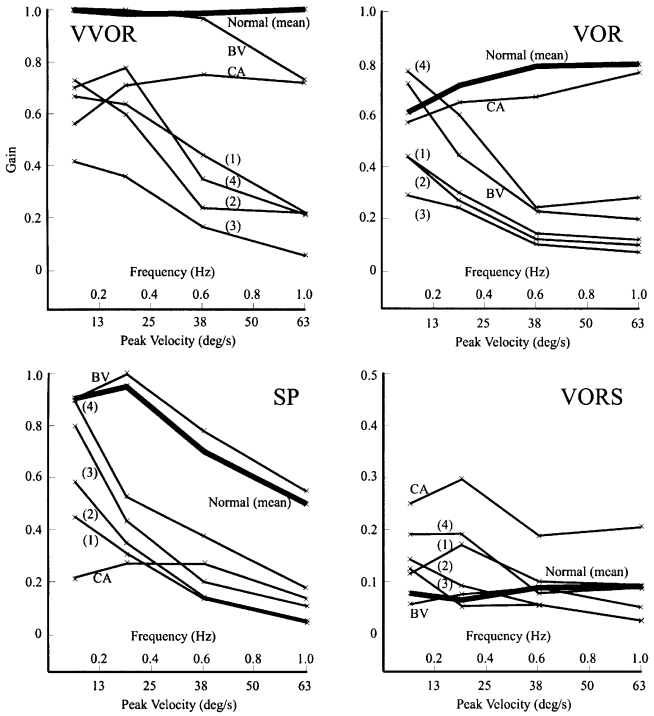


Fig. 5 The gains of the horizontal VVOR, VOR and VORS as a function of the frequency and velocity of head rotation during head-on-trunk testing and the gain of SP as a function of target frequency and velocity. Mean data from the four normal subjects are shown in thick black lines. Individual data from the CABV patients (1–4), from the CA patient and from the BV patient are shown in thin black lines. In normal subjects, VVOR gain stays constant at 1.0, VOR gain rises from ~0.6 at 0.1 Hz and 10°/s peak velocity, to 0.80 at 1.0 Hz and 63°/s peak velocity; VORS stays at <0.1, SP gain drops from ~0.95 to ~0.5 over the same dynamic range. In the CA patient, VOR gain is close to normal, SP gain is only ~0.25 throughout the test range, VORS gain is abnormally high from 0.2 to 0.3 and VVOR gain rises only slightly from a low 0.57 to slightly less low 0.68. Although at the lowest stimulus frequency, VOR gain is normal in one of the four CABV patients and SP gain is also normal or near-normal in two of the four CABV patients, all three measures, VOR, SP and VVOR gain, in all four CABV patients decline as a function of stimulus frequency and velocity so that by 0.6 Hz all gains in all patients are less than half the normal value. VORS is abnormally high at the lowest stimulus frequency in three of the four CABV patients but appears to be normal at the higher frequencies since there is less VOR to suppress.

1 Hz. In the BV patient, the mean VOR gain was 0.72 at 0.1 Hz, decreasing to 0.21 at 1 Hz. The VOR gain in the CA patient was not significantly different from that in normals: 0.57 at 0.1 Hz increasing to 0.87 at 1 Hz.

VVOR

The VVOR gains in CABV patients were lower than those in normal subjects and, in contrast to normal subjects, gain decreased with increasing stimulus frequency (Figs 2, 4 and 5). In normal subjects, the mean VVOR gain was close to 1.0 at all frequencies tested: 1.01 ± 0.01 at 0.1 Hz and 1.01 ± 0.03 at 1 Hz. In the CABV patients, the mean VVOR gain was 0.63 ± 0.14 at 0.1 Hz, decreasing to 0.19 ± 0.08 at 1 Hz. In the CA patient, the mean VVOR gain was also low, 0.57 at 0.1 Hz, but, unlike in the CABV patients, increased rather than decreased with increasing stimulus frequency, to 0.68 at 1 Hz, a value closer to the normal range. In the BV patient, VVOR gain was 1.02 at 0.1 Hz (normal) but decreased to 0.71 at 1 Hz (less than normal). The VVOR gain in CABV patients was, on average, larger than either VOR or SP gain alone. The VVOR gain was approximately equal to VOR gain plus SP gain modulated by the gaze velocity error (Fig. 4).

VORS

The VORS test (Fig. 1) was normal (gain <0.1) in all four CABV patients and in the BV patient at the two higher test frequencies (0.6 and 1.0 Hz) and only abnormal (gain = 0.13–0.20) at the two lower test frequencies (0.1 and 0.3 Hz) in two of the four CABV patients. Note that a subject with low VOR gain will also have a low VORS gain. In contrast, VORS was abnormal (gain = 0.2–0.3) at all test frequencies in the CA patient.

SP

The SP gains of CABV patients and of the CA patient were lower than those of normal subjects and, as in normal subjects, decreased with increasing stimulus frequency (Fig. 1). In normal subjects, the mean SP gain was 0.92 ± 0.06 at 0.1 Hz, decreasing to 0.50 ± 0.10 at 1 Hz. In the CABV patients, the mean SP gain was 0.69 ± 0.20 at 0.1 Hz, decreasing to 0.09 ± 0.07 at 1 Hz. In the CA patient, the mean SP gain was 0.21 at 0.1 Hz, decreasing to 0.14 at 1 Hz. The SP gain in the BV patient was not significantly different from that in normals: 1.01 at 0.1 Hz decreasing to 0.55 at 1 Hz.

Compensatory saccades

During VVOR testing, all the CABV patients made clinically obvious bursts of saccades which compensated for the position error caused by the gaze instability, the clinical sign of an impaired VVOR (Figs 1 and 2). Since peak saccade velocity is a function of saccadic amplitude (Bahill *et al.*, 1975), saccade velocity is a useful index of gaze position error. The CABV patients produced more saccades and bigger saccades than did normal subjects, the CA patient or the BV patient, particularly at 0.6 Hz. During this task, all the CABV patients reported difficulty focusing on the target at ⩾0.6 Hz, whereas control subjects reported no such difficulties at any frequency.

Head-and-trunk rotations

Gaze-evoked nystagmus

At 15° left and right gaze, each of the patients had just recordable gaze-evoked nystagmus of <2°/s average slow-phase velocity.

VOR

In each of the four CABV patients, VOR gain was <0.20 at both 0.1 and 0.33 Hz (Fig.3). In this routine clinical test, our laboratory normal values are 0.38 ± 0.18 (2 SD) at 0.1 Hz and 0.45 ± 0.20 (2 SD) at 0.33 Hz.

VVOR

In each of the four CABV patients, VVOR gain at both 0.1 and 0.33 Hz was <0.5 (Table 1 and Fig. 3). In this routine clinical test, our laboratory normal value is >0.95.

VORS

In each of the four CABV patients, VORS gain at both 0.10 and 0.33 Hz was normal (<0.1). Note that a subject with low VOR gain will also have a seemingly normal low VORS gain (Table 1).

OKR

In each of the four CABV patients, OKR gain at the stimulus velocity of 50°/s was <0.2 (Table 1). In this routine clinical test, our laboratory normal value is >0.4.

Discussion

The clinical sign of VVOR impairment

We studied four patients with idiopathic progressive CABV and report the oculographic features of the characteristic clinical sign of this new syndrome: an impaired VVOR. To test the VVOR, or doll's head reflex, the patient need only stare at an earth-fixed target while slowly and smoothly turning their head from side to side or up and down. Normal subjects and patients with loss only of the VOR or only of SP + OKR can nonetheless still make smooth compensatory eye movements and maintain gaze. In contrast, only patients with loss of both the VOR and SP + OKR are unable to make fully compensatory smooth eye movements and must make a series of observable saccades in the compensatory direction to maintain gaze.

Normally, subjects with impaired SP also have impaired VORS (Grant *et al*., 1992), which can easily be tested clinically (Halmagyi and Gresty, 1979). However, in CABV patients, while SP is genuinely impaired, VORS will appear to be normal since there is little or no VOR to suppress.

Although our CABV patients had VVOR impairment in all directions, it is possible that there are patients in whom the VVOR impairment would be only horizontal or only vertical. For example, a patient with a brainstem lesion involving both medial longitudinal fasciculi would have a defective vertical VOR (Ranalli and Sharpe, 1988), a normal horizontal VOR, at least in the abducting eye (Cremer *et al*., 1999), and would have impairment of vertical SP either from the medial longitudinal fasciculus lesions or from involvement of cerebellar pathways in the brainstem or in the cerebellum itself. Such a patient would have selective impairment of only the vertical VVOR. It is also theoretically possible to have a unidirectional VVOR impairment in a patient with BV and a unidirectional SP + OKR impairment. In contrast, in a patient

Table 1 *Values for the VVOR and VOR during head-and-trunk oscillations at 0.1 and 0.33 Hz in a rotating chair, and for the OKR tested as optokinetic nystagmus at 50°/s, in four CABV patients, in an isolated BV patient and in laboratory normal values.*

Patients	Head-and-trunk				
	VVOR gain		VOR gain		OKR gain
	0.1 Hz	0.33 Hz	0.1 Hz	0.33 Hz	
CABV(1)	0.21	0.48	0.16	0.19	0.10
CABV(2)	0.28	0.23	0.11	0.14	0.04
CABV(3)	0.08	0.11	0.02	0.08	0.05
CABV(4)	0.23	0.40	0.05	0.04	0.07
BV	0.85	0.80	0.01	0.09	0.51
Normal	>0.95	>0.95	0.38	0.45	>0.40

The differences between the CABV patients and the normal subjects, are evident at both tested frequencies. Note that CABV patients are the only individuals with low VVOR gain and the only ones with low gain for all three reflexes: VVOR, VOR and OKR.

Table 2 *Data for normal subjects during head-on-trunk oscillations at 0.1 Hz and 6°/s, 0.3 Hz and 19°/s, 0.6 Hz and 38°/s and 1 Hz and 63°/s.*

	VVOR				VOR				SP			
	Eye velocity (°/s)	Gain	Saccade frequency (sac/s)	Saccade amplitude (°): velocity (°/s)	Eye velocity (°/s)	Gain	Saccade frequency (sac/s)	Saccade amplitude (°): velocity (°/s)	Eye velocity (°/s)	Gain	Saccade frequency (sac/s)	Saccade amplitude (°): velocity (°/s)
0.1 Hz and 6°/s												
Patients												
CABV(1)	4.3	0.67	4.7	1.5: 65	4.3	0.42	1.8	2.1: 78	3.6	0.58	3.5	1.2: 61
CABV(2)	5.7	0.73	2.5	1.1: 8	3.6	0.42	1.7	1.4: 67	5.0	0.80	2.1	0.7: 40
CABV(3)	3.6	0.42	3.0	1.8: 47	2.8	0.27	1.9	2.5: 70	2.9	0.46	2.5	2. 7: 54
CABV(4)	7.9	0.70	1.5	0.9: 60	6.4	0.75	1.2	1.7: 81	5.7	0.91	2.0	1.1: 48
CA	5.2	0.57	3.1	0.7: 43	6.3	0.57	3.1	1.1: 37	1.3	0.21	2.5	2.2: 69
BV	13.3	1.02	2.2	0.6: 21	6.2	0.72	2.9	1.2: 55	7.2	1.11	2.1	0.8: 20
Normals												
1	8.6	1.02	2.6	2.0: 21	4.3	0.61	1.3	1.1: 34	5.7	0.91	0.9	0.5: 23
2	8.8	1.01	2.2	1.0: 24	3.5	0.56	1.2	1.0: 38	5.2	0.83	2.2	1.1: 31
3	5.5	1.00	2.7	0.8: 13	4.8	0.61	1.6	0.7: 20	6.0	0.96	2.6	0.8: 21
4	6.7	1.02	0.2	1.3: 43	3.9	0.70	0.1	3.0: 119	6.1	0.97	0.5	0.7: 24
0.3 Hz and 19°/s												
Patients												
CABV(1)	12.9	0.64	3.7	1.3: 65	7.1	0.28	4.5	2.4: 95	6.9	0.36	3.8	3.2: 126
CABV(2)	12.8	0.60	3.8	1.6: 73	4.3	0.25	2.3	0.8: 58	8.1	0.43	2.7	1.5: 100
CABV(3)	6.4	0.36	4.5	2.4: 78	5.7	0.22	2.4	2.5: 73	5.6	0.30	2.9	3.5: 97
CABV(4)	15.7	0.78	2.5	1.4: 79	9.8	0.58	2.4	3.3: 100	10.0	0.53	2.5	1.5: 89
CA	18.5	0.71	3.2	1.1: 58	16.0	0.65	2.8	2.2: 34	5.4	0.28	3.6	2.5: 91
BV	26.3	1.01	2.5	0.9: 31	18.5	0.44	4.1	2.7: 93	19.1	1.01	2.5	1.0: 40
Normals												
1	22.1	1.04	1.2	1.0: 29	17.9	0.72	1.9	0.8: 26	18.3	0.97	1.6	0.9: 34
2	21.2	1.06	1.5	0.5: 29	11.5	0.60	2.5	0.5: 54	16.7	0.89	2.1	1.0: 41
3	19.5	0.98	2.1	0.7: 16	17.3	0.62	1.1	0.8: 21	17.4	0.92	2.8	0.8: 38
4	21.7	1.01	0.9	0.5: 17	18.2	0.76	0.1	1.0: 59	18.7	0.99	0.6	0.5: 20
0.6 Hz and 38°/s												
Patients												
CABV(1)	15.7	0.44	4.6	2.8: 98	5.6	0.12	4.7	2.2: 91	5.7	0.15	4.1	4.4: 176
CABV(2)	15.7	0.24	4.6	4.5: 109	5.4	0.10	3.4	3.0: 81	7.4	0.20	2.5	9.7: 230
CABV(3)	5.7	0.17	4.4	1.9: 91	5.0	0.08	1.9	1.9: 95	5.3	0.14	3.6	4.2: 119
CABV(4)	17.1	0.35	3.2	6.1: 182	13.9	0.22	2.1	3.6: 119	14.3	0.38	3.5	4.7: 152
CA	27.7	0.75	3.3	0.9: 83	24.1	0.67	1.8	0.7: 31	10.7	0.28	4.4	4.5: 191
BV	52.3	0.97	1.8	1.5: 72	18.2	0.24	3.6	2.0: 67	29.3	0.78	4.1	1.7: 51
Normals												
1	31.4	1.05	1.1	0.2: 7	45.2	0.79	1.2	0.7: 35	24.3	0.64	1.7	1.0: 39
2	43.5	1.05	1.0	0.4: 31	24.2	0.64	1.5	1.5: 70	31.3	0.83	1.7	2.2: 63
3	35.5	0.98	1.2	0.3: 16	37.3	0.83	2.1	0.9: 65	26.7	0.71	2.9	1.6: 65
4	38.7	0.99	0.3	0.3: 40	29.9	0.79	0.1	1.2: 108	25.3	0.67	1.6	2.0: 62
1.0 Hz and 63°/s												
Patients												
CABV(1)	18.5	0.23	3.9	5.9: 153	7.1	0.10	4.6	2.5: 55	2.2	0.04	3.4	17.0: 231
CABV(2)	14.8	0.23	3.8	6.9: 118	6.4	0.08	3.2	2.2: 89	7.3	0.12	2.9	10.1: 244
CABV(3)	4.3	0.06	4.0	1.4: 40	3.8	0.05	2.0	4.2: 95	2.1	0.03	3.1	5.0: 125
CABV(4)	16.4	0.22	2.9	16.0: 250	20.0	0.26	2.1	3.1: 149	11.4	0.18	3.4	6.0: 176
CA	40.4	0.68	2.7	0.8: 91	58.7	0.87	4.6	2.5: 55	8.5	0.14	3.7	6.0: 216
BV	68.3	0.71	4.7	2.7: 203	19.1	0.21	3.9	2.6: 131	34.7	0.55	4.2	2.0: 122
Normals												
1	56.8	1.05	1.7	0.6: 10	60.3	0.80	1.3	0.5: 28	27.1	0.43	1.8	2.0: 111
2	50.2	1.01	0.3	0.3: 43	48.4	0.74	1.6	0.6: 89	37.5	0.60	1.6	2.2: 122
3	53.5	1.01	1.1	0.4: 29	51.7	0.73	1.6	1.6: 48	35.8	0.57	3.3	2.8: 129
4	61.7	0.97	0.3	0.2: 43	61.0	0.82	0.4	2.0: 163	24.5	0.39	3.1	2.1: 149

Values are given for smooth eye velocity, velocity gain and for compensatory saccade frequency, mean amplitude and mean velocity. The data is also shown graphically in Figs 4 and 5.

with a unilateral vestibulopathy and bidirectional SP + OKR loss, VVOR impairment will be inapparent during head rotations that are slow enough to be within the normal operational range of SP + OKR, i.e. <1 Hz or 100°/s, because a unilateral VOR impairment becomes evident only with head rotations above ~2 Hz and 200°/s (Cremer *et al*., 1998; Lasker *et al*., 2000).

The site of lesion producing VVOR impairment

Although VOR impairment is generally due to disease affecting vestibular end-organs or vestibular nerves bilaterally (Brandt, 1996; Rinne *et al*., 1998), e.g. gentamicin toxicity (Halmagyi *et al*., 1994), it can sometimes occur due to lesions or diseases of the brainstem. In contrast, SP + OKR impairment is always due to brainstem or cerebellar dysfunction (Ranalli and Sharpe, 1988; Johnston *et al*., 1992; Büttner *et al*., 1998). The combined impairment of VOR and SP + OKR suggests a combined lesion of the cerebellum and brainstem, involving the vestibular nuclei. In support of this proposal is the morphological observation that the vestibular nuclei are involved in the olivopontocerebellar form of MSA. However, the involvement is not specific and is part of a generalized brainstem atrophy (Wenning *et al*., 1994, 1997). There are reports of temporal bone pathology in hereditary ataxia (Spoendlin, 1974), but clinically (van Boegart and Martin, 1974) these cases are very different from the CABV patients described here and there are no reports of temporal bone pathology in olivopontocerebellar atrophy or MSA. For the time being, the site of the lesion responsible for the BV in CABV remains speculative.

What disease do CABV patients have?

While the disease progression in CABV patients is consistent with that seen in degenerative ataxias (Klockgether *et al*., 1998), the clinical pattern does not fit any single presently accepted nosologic entity. None of our patients had evidence of any known acquired cause of CA such as alcoholism, malignancy or gluten sensitivity. Although none had a family history of ataxia or any other progressive neurological disorder, could they nonetheless have had a hereditary ataxia? Although the VOR and SP + OKR are impaired in SCA1 (Bürk *et al*., 1999) and SCA3 (Büttner *et al*., 1998; Bürk *et al*., 1999; Gordon *et al*., 2003), genetic testing was negative for SCA 1, 2, 3, 6 and 7 in all four CABV patients. The VOR can also be impaired in typical Friedreich's ataxia (Moschner *et al*., 1994) although it has not been reported to be absent, as in the four CABV patients, or to be a presenting feature as in one of the CABV patients here. In Friedreich's ataxia, the bilateral vestibular impairment is accompanied by bilateral deafness (Ell *et al*., 1984). All our patients had negative Friedreich's ataxia repeat genetic testing, although this does not exclude an unusual mutation in the Friedreich's ataxia gene (McCabe *et al*., 2002; Pandolfo, 2001). VVOR impairment can also occur in Wernicke's encephalopathy (Furman and Becker, 1989; Leigh and Zee 1999; and the video available at *Brain* Online), but it was clinically evident that none of our patients had this disease. The VOR can also be impaired in patients with the OPCA form of MSA (Moschner *et al*., 1994), but none of our patients had significant orthostatic hypotension or extrapyramidal features, so that they did not fulfill the currently accepted criteria for the diagnosis of MSA (Gilman and Quinn, 1996; Gilman *et al*., 1999). Furthermore, the progression of the disease seems slower and more benign in CABV than in MSA (Watanabe *et al*., 2002). This was also the case with one of the two patients in the first report of this condition (Bronstein *et al*., 1991). It is also possible that the relationship between the CA and the BV was simply coincidental. These patients might have both the well known idiopathic late-onset CA (Abele *et al*., 2002) and the less well known idiopathic BV (Rinne *et al*., 1998). A similar VVOR impairment could be expected in elderly patients with impaired SP (Sharpe and Sylvester 1978), who also develop BV, for example due to gentamicin toxicity.

Head-on-trunk versus head-and-trunk VVOR testing

In all CABV patients, the VVOR gain was abnormally low during both head-on-trunk and head-and-trunk testing. Although we found significant VVOR gain differences between these two paradigms, this probably can be explained by differences in the maximum chair velocities between the tests (head-and-trunk: ±50°/s at both 0.1 and 0.33 Hz; head-on-trunk: 6°/s at 0.1 Hz to 63°/s at 1.0 Hz).

We think that the cervico-ocular reflex made no significant contribution to VVOR gain during head-on-trunk testing. In normal subjects, the cervico-ocular reflex contributes little to gaze stability; its gain is normally <0.1 (Sawyer *et al*., 1994). In BV patients, cervico-ocular reflex gain increases up to 0.5 (Bronstein and Hood, 1986). However, in BV patients with reduced SP + OKR gain, similar to the patients reported here, Bronstein *et al*. (1991) found that the cervico-ocular reflex gain is the same as in normal subjects.

During rotatory chair (head-and-trunk) testing and during bedside (head-on-trunk) testing in this study, the patient viewed a visual scene and thereby had an optokinetic stimulus, whereas during the search coil head-on-trunk testing there was no scene but only a fixation target and therefore only an SP stimulus. Nevertheless, both head-on-trunk and head-and-trunk test paradigms clearly showed that in CABV patients the VVOR gain was less than normal; therefore, either of these stimuli could be used to test VVOR impairment.

VVOR

Our data suggest that it is the SP reflex or the closely related fixation reflex that enhances or boosts the VOR (at head

rotation frequencies of <1 Hz) in order to produce a VVOR gain that is close to 1.0 from ~0.1 to 6 Hz (Leigh *et al*., 1994). In our BV patient during head-on-trunk rotation, VOR gain dropped from 0.72 at 0.1 Hz to 0.26 at 0.6 Hz; however, VVOR gain stayed close to 1.0 (Fig. 5). In contrast, in our CA patient with impaired SP, both VOR and VVOR gain stayed between ~0.6 and 0.7 in the same stimulus frequency range.

Our data also show that patients who have impaired, but not absent, VOR and SP can nonetheless enhance their residual VOR with their residual SP to produce a VVOR with a higher gain than VOR or SP alone. If SP is driven by retinal velocity error (retinal 'slip'), then VVOR gain should be approximated by VVOR = VOR + (1 – VOR) × SP. Although this linear function is not the complete explanation, it does produce a reasonable approximation of the data in two of the four CABV patients (Fig. 4).

In summary, we have shown that when both VOR and SP are impaired, the VVOR cannot produce fully compensatory smooth eye movements so that when CABV patients rotate their heads while viewing a space-fixed target, they produce gaze position errors, and lose the target, which they then reacquire with a clinically observable burst of compensatory gaze position error-correcting saccades: the characteristic clinical sign of CABV.

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