Eye Movements in a Familial Vestibulocerebellar Disorder

By Ch. M. Harris, Jane Walker, Fatima Shawkat, J. Wilson and Isabelle Russell-Eggitt

1Department of Ophthalmology, 2Department of Neurology, Hospitals for Sick Children, Gr. Ormond Street, London, UK

Abstract

Eye movement abnormalities consisting of poor or absent smooth pursuit and vestibulo-ocular reflex suppression, gaze-paretic and rebound nystagmus, slow build-up of optokinetic nystagmus, mildly hyperactive vestibulo-ocular reflex, and a high incidence of strabismus were inherited in an autosomal dominant fashion in 10 members of a non-consanguineous English caucasian family. The onset was in early childhood, but was not congenital. In 7 cases there was no tremor, dizziness, consistent ataxia, or other cerebellar signs that are often associated with these ocular motor deficits, and apart from strabismus, patients were asymptomatic. Magnetic resonance imaging of the propositus was normal. After childhood there appears to be no progression, with the oldest affected member being 40 years. Two members had been prone to falling in childhood, and one admitted to dizziness when tired. This condition, which is probably benign, has not been previously described and may represent a very mild variant of episodic ataxia or a new vestibulocerebellar syndrome.

Key words

Nystagmus – Smooth pursuit – Optokinetic – Autosomal dominant – Episodic ataxia

Introduction

Abnormal eye movements acquired in childhood are of concern since they often indicate intracranial disease. A 7-year-old boy, whose mother had been diagnosed with neurofibromatosis type-1 (NF1), presented with cutaneous stigmata and Lisch nodules of the irides, gaze-paretic nystagmus (GN), rebound nystagmus (RN) and saccadic pursuit. Despite these vestibulocerebellar ocular motor signs, he had no ataxia and neuro-imaging showed no abnormality. Investigation of his family revealed similar eye movement abnormalities, but no stigmata of NF1, in his father, younger sister, and 7 other paternal relatives, whereas his mother had normal eye movements. It was concluded that this boy had inherited NF1 from his mother, but that the eye movement abnormalities were unrelated and inherited from his father.

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Horizonal eye movements were recorded using dc-coupled electro-oculography from the propositus, his unaffected mother, his affected father, and 4 affected and 6 unaffected paternal relatives. A further 4 paternal relatives were deduced to be affected from their medical records, but did not have eye movements recorded.

Horizontal optokinetic nystagmus (OKN) was elicited by a full-field brightly coloured high contrast curtain rotated at 25 and 50 deg/s in both directions. The horizontal vestibular-ocular reflex (VOR) was tested by sustained rotation in the dark at 80 deg/s for 40s with an acceleration/deceleration of 18 deg/s/s. Smooth pursuit (SP) was elicited by ramping a large target horizontally at a constant speed of 10, 20, 30, or 40 deg/s through a total angle of 40 degrees symmetrically about the midline, with a 1.5 s pause at the end of each excursion. VOR suppression was tested by rotating the chair with the SP target. This was carried out in the light so that fixation of the target also required the patient to suppress the optokinetic response to the laboratory background; normal children and adults accomplish this task with no difficulty. Saccades were elicited by small light-emitting diodes or large toys depending on the age and cooperation of the patient. The horizontal neural integrator time-constant was estimated from the centripetal drift during eccentric fixation in the dark (19, p. 183).

Family

The family was of English ancestry with no consanguinity (Fig. 1). The paternal grandmother (1.2) was the oldest surviving member and was not affected. We have little information on the paternal grandfather (1.1): he rode a bicycle, had “normal” vision on entering the army catering corps, and did not wear spectacles until middle age. He died at 80 years from lung cancer and there was no indication of ataxia.

Apart from strabismus and nystagmus, the medical histories of affected members were mostly unremarkable. However, the father (II.4) of the propositus admitted to blurry vision and dizziness and unsteadiness of gait when tired. As a child, an aunt (II.2) had been prone to falling of unknown etiology. An uncle (II.10) had been extensively investigated at the age of 3 for late attainment of motor milestones, torticollis, nystagmus, and a tendency to lose his balance and pitch forward. No diagnosis was made. A cousin (III.4) was reported to be clumsy and mildly hypotonic at 3 years of age. We describe here only the case history of the propositus.
Case III.11 7 years (Propositus)

Delivery was full-term with a normal birthweight. There was no significant perinatal history, but by 12 weeks he was failing to thrive. At 1 year he contracted meningitis. At 4.5 years, there was an intermittent right esotropia. Vision was 6/12 in the right and 6/6 in the left eye and occlusion was begun resulting an acuity of 6/6 in each eye. At 6 years a chin-down head posture and horizontal nystagmus that occurred on converging to near point was first noted. Vision was still 6/6 as assessed by the Kay pictures as he was not yet reading. At this time he was also treated with growth hormone for pituitary hypofunction.

Upon examination at 7 years, when NF1 was diagnosed in his mother, he had 6 café-au-lait macules, one axillary freckle, and Lisch nodules of the irides. Optic discs and visual fields were normal. Electroretinograms were normal, but pattern visually-evoked potentials were attenuated and degraded. Computed tomography (CT) of the brain, including imaging of the chiasm, was normal. At this time he was referred for eye movement recordings.

GPN was recorded in horizontal and elevated gaze. The nystagmus was unaltered by monocular viewing. In the dark the decay of eye position indicated an integrator time-constant of about 1–2 s. RN was also noted. Tracking of the large SP target was completely saccadic (Fig. 3), and there was no VOR suppression. Full-field OKN had a slow build-up with a gain of about 0.4. It was not possible to obtain a reliable measure of monocular OKN gain because of the presence of curvilinear slow phases (see Discussion). Vestibular nystagmus was asymmetrical to sustained rotation with a gain of 1.1 for leftward slow phases and 0.7 for rightward; the time-constant was 15 s in either direction.

It was concluded that there was a complete SP deficit, which also explained the lack of VOR suppression and the slow build-up of OKN, and the neural integrator had an abnormally short time-constant. These findings strongly suggested a cerebellar disorder, but magnetic resonance imaging (MRI) of the posterior fossa revealed no abnormality. At this time it was discovered that his father, sister, and other paternal relatives had similar ocular motor deficits, but that his mother’s eye movements were normal. It appeared, therefore, that the ocular motor deficits were inherited from his father instead of his mother, and were unrelated to NF1.

Results and discussion

The clinical and ocular motor findings of affected family members are summarised in Table 1. The medical records of the 4 relatives who did not have eye movements recorded (II.11, III.2, III.4, III.13) revealed a history of "nystagmus on version", which was assumed to be GPN.

It was quite clear that the affected members of this family had very similar eye movement abnormalities, consistent with an autosomal dominant pattern of inheritance. The unaffected had normal eye movements. The ocular motor deficits consisted of nystagmus (horizontal and upbeat GPN, and RN), poor or absent SP, lack of VOR suppression, abnormal OKN, and elevated VOR gains. There was also a strong incidence of strabismus among the affected members. Based on medical records, the onset was in childhood but probably not before 1 year. In one case (III.12), the onset of GPN was confirmed to be after the third year. CT of the brain and MRI of the posterior fossa revealed no abnormality in the propotus.

Nystagmus

All affected individuals exhibited GPN; the nystagmus was unaltered by monocular occlusion and reversed its direction when either eye moved through primary position and, therefore, was not manifest latent nystagmus. The presence of RN in some patients indicated a central rather than a neuromuscular or myopathic origin.

Central GPN results from poor gaze-holding ability due to neural integrator dysfunction (NID). In NID the integrator does not maintain sufficient tonic innervation to the extra-ocular muscles at the desired eccentricity, and the eyes are pulled back to primary position by viscoelastic forces of the globe and musculature. Repeated centrifugal saccades are then needed to re-foveate the target. In our patients the integrator time-constant ranged from 1–5 s, which is abnormally short.
RN was present in 4 out of the 6 patients that were recorded from. RN is frequently found in conjunction with GPN (34). The mechanism behind RN is not known, but it is thought to reflect a bias during attempted eccentric fixation (32). An exceptionally clear picture of this bias in the dark without the usual obscurations from saccades is shown in Figure 2. Here, in attempted eccentric fixation, the eyes do not decay all the way back to primary position but to some intermediate position. Presumably the null of the integrator has shifted in the direction of attempted gaze. This would explain why the GPN gradually decays on sustained eccentric fixation; the null moves and the effective eccentricity (eye position – null position) decreases. When primary position is quickly re-fixed, the eye becomes eccentric relative to the current position of the integrator null, thereby inducing a “rebound nystagmus”, which is really GPN in the reverse direction.

RN is usually considered a sign of cerebellar disease (16) and has been reported in association with a tumour confined to the flocculus (32). RN has been reported in cases of cerebellar atrophy (2, 15, 16, 34), spino-cerebellar degenerations (31), cerebellar lesions (15, 16), cerebellar cortical atrophy (37), multiple sclerosis (16), cerebellitis (33), olivocerebellar atrophy (6), demyelinating disease (15), drug intoxication (1, 15), giant axonal neuropathy (18), Charcot-Marie-Tooth (10), Gerstmann-Sträussler-Scheinker disease (11), hemiplegic migraine, nystagmus and tremor (38), and episodic vertigo and ataxia (4, 26). RN can also occur in normals after prolonged far eccentric fixation (24). However, there are no reports of inherited physiologic RN; moreover physiologic RN is not associated with other ocular motor deficits.

**Smooth pursuit**

The second notable ocular motor deficit in these cases was the bilaterally absent, or very poor SP (Figure 3). The presence of SP was not examined clinically, so it is not known whether the SP deficit occurred simultaneously with the onset of nystagmus. Poor SP is often associated with a
commensurate inability to suppress the VOR reflex (34). All of our affected patients were unable to suppress their VOR. The SP deficit is functionally distinct from NID. A leaky integrator cannot, itself, disable VOR suppression, because in successful suppression the eyes do not deviate from primary position (where the integrator has negligible effect). Also NID cannot cause slow build-up of OKN.

The cerebellum is involved in the control of SP. Cerebellectomy abolishes SP (30). Flocculectomy in the monkey reduces SP gain by a third, although does not abolish it (36). Therefore, the complete absence of SP in some of our patients may imply that the deficit involves other cerebellar structures as well ([19] p. 157). The posterior vermis has also been implicated in the control of SP (22, 25). Lesions of the posterior vermis are also associated with saccade dysmetria (23), which was not found in any of our patients.

**Optokinetic nystagmus**

Affected individuals who had absent SP also exhibited slow build-up of OKN, whereas one patient (III.12) with residual SP showed fast OKN build-up. This is consistent with the notion that there are two components to OKN: a fast (immediate) component driven by or at least closely associated with the SP system (35) and a slow, velocity storing component (8). Two patients (II.2, II.10) appeared to have fast OKN build-up even though their SP was absent. In fact this was a “pseudo-OKN”, because at the beginning or reversal of curtain rotation, there was a saccadic shift in gaze away from primary position in the opposite direction of curtain rotation. This induced a GPN with slow phases in the same direction as curtain rotation, and may have substituted for OKN. As shown in Figure 4, when the eyes approach primary position this pseudo-OKN disappeared; true OKN appears later after a substantial build-up time. Varying degrees of contraversive deviation with an ensuing GPN were adopted frequently by our affected patients during OKN stimulation.

Even after true OKN was established, the slow phases were often curvilinear. We attribute this to the failure of the integrator to establish the correct eye velocity at all eccentricities compounded with low gain OKN. Thus, OKN slow phases have augmented velocities when approaching the integrator null and attenuated velocities when moving away from the null, and appear similar to GPN. The distinction between true OKN and GPN was frequently difficult to make, particularly in the propositus who tended to have large amplitude OKN (as most children do), which induced very curvilinear slow phases, even GPN with slow phases in the opposite direction to curtain motion. The OKN gains reported here were based on the slopes of linear portions of slow phases.

Monocular OKN was asymmetric in most affected individuals: gain was markedly less in the nasotemporal (n-t) than in the temporalnasal (t-n) direction. Monocular asymmetries are usually caused by interference in binocular development (strabismus, anisometropia, cataract) in the first few months of infancy (21). It is tempting to conclude, therefore, that the strabismus in these cases really had an early onset (i.e. in the first 6 months) rather than later in childhood when they

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**Fig. 3** Tracking behaviour in smooth pursuit task. Target was ramped through 40 degrees horizontally symmetrically around primary position at 10 deg/s, with a 1.5 s pause at the end of each excursion. Top trace shows normal smooth pursuit from the propositus’ mother. Other traces recorded from propositus and affected paternal relatives. The propositus’ sister demonstrated some low gain smooth pursuit. All others showed only saccadic tracking.

**Fig. 4** Full-field horizontal optokinetic response to curtain rotated at 25 deg/s in both directions (bottom trace). Top trace: normal binocular response from propositus’ mother. Middle trace: abnormal binocular response from paternal uncle (II.10) showing low amplitude OKN with slow build-up. Arrows: (a), (b) shift of gaze in opposite direction of curtain rotation; (c) gaze-paretic nystagmus with slow phases in same direction as curtain rotation (pseudo-OKN); (d) true OKN after slow build-up.
presented. However, this deduction is complicated by the absence of fast-OKN, which may contribute more to n-t OKN.

Vestibulo-ocular reflex

The time-constants of the VOR to sustained rotation were normal; there was no perseverance of nystagmus that has been reported in monkeys following nodulectomy (29). However, the VOR gains were abnormally high, being close to unity. High gains have been reported in lesions of the vestibulocerebellum (3, 27, 36), and the flocculus appears to be involved in the adaptive control of VOR gain (20). However, we have not tested for the presence of VOR adaptation, and cannot rule out the possibility that the near-unity VOR gains in our affected patients are an adaptive compensation for the lack of fast-OKN.

Clinical aspects

This constellation of ocular motor defects in the affected members of this family can be attributed to three distinct central abnormalities: NID (with RN), poor or absent SP, and mildly hyperactive VOR. Although we have no radiological or pathological evidence, the many clinical reports and animal studies make a strong case for locating these abnormalities in the vestibulocerebellum, probably the flocculus and paraflocculus. Similar dominantly inherited ocular motor deficits are described in hereditary cerebellar ataxia (17, 34), Machado-Joseph’s disease (9), spinocerebellar degeneration (31), and Gerstmann-Sträussler-Scheinker disease (11). However, in our patients, the early-onset, lack of progression after childhood, and the absence of any non-oculomotor neurological signs in most of our cases are not compatible with these conditions.

Similar eye movement deficits have also been reported in autosomal dominant episodic/periodic/paroxysmal ataxia (4, 12, 14). This rather diffuse, usually non-progressive, and heterogeneous condition has a variable onset (often in childhood), and is characterised by episodic attacks of ataxia which may be accompanied by dysarthria, vertigo, dizziness, nausea, or vomiting. MRI is usually normal although atrophy of the cerebellar vermis has been reported (28). The hallmark of this condition is its responsiveness to acetazolamide, although the interictal ocular motor abnormalities remain unaffected. In a possibly related condition, Theunissen et al (26) reported a non-progressive “familial vestibulocerebellar dysfunction” in a mother and two daughters who exhibited eye movements abnormalities similar to those in our patients, with no ataxia or other cerebellar signs. As with our propositus, neuroradiology showed no abnormality. However, their patients suffered from attacks of dizziness, which was the presenting symptom in their propositus. They also attributed their findings to an unknown disorder of the vestibulocerebellum (flocculus and nodulus). In another probable variant, Furman et al (13) have reported a dominantly inherited non-progressive infantile condition in which mild gait ataxia was associated with GPN. MRI indicated localised atrophy of the anterior vermis. Their patients also had upbeat nystagmus in primary position.

Two of our patients (II.2, II.10) were reported to be susceptible to falling in childhood, and after direct questioning, another admitted to dizziness when tired in adulthood (II.4). It is not clear whether these constitute episodes of ataxia and vertigo. Nevertheless, the remaining 7 affected members appeared to have had no such attacks, and it is difficult to justify the label of episodic ataxia in so many asymptomatic cases. Because of the lack of attacks, any possible effects of acetazolamide could not, of course, be tested. Thus, it seems that this condition is either an extremely mild variant of autosomal dominant episodic ataxia but with the typical interictal eye movement abnormalities, or it is a new vestibulocerebellar disorder with minimal or no ataxia.

In conclusion, this family exhibited autosomal dominantly inherited ocular motor abnormalities, which are probably caused by a vestibulocerebellar anomaly. A notable feature was the absence of symptomatic ataxia or any other cerebellar sign. The condition appears to be non-progressive after childhood (the oldest affected member is 40 years), and except a high incidence of strabismus there were no visual symptoms. This family illustrates the usefulness of examining family members when investigating a child who presents with “cerebellar” eye movement abnormalities.

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Dr. Ch. M. Harris

Department of Ophthalmology
Hospitals for Sick Children
Great Ormond Street
London WC1 N3 JH, UK