Diagnosing children presenting with asymmetric pendular nystagmus

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Nystagmus is usually conjugate, with the same amplitude, frequency, and direction in each eye. If there are interocular differences it is called asymmetric, dissociated, or disconjugate. It can be absent in one eye, but more commonly it is just much more marked in one eye compared with the other. Asymmetric pendular nystagmus in the primary position may occur in any axis and is reported in the literature to occur in one of three situations: secondary to an intracranial lesion usually involving the chiasm or midbrain, secondary to late onset monocular visual loss, and as part of the triad of signs which constitutes spasmus nutans.

Spasmus nutans is a retrospective diagnosis of a self-limiting, benign condition consisting of asymmetric pendular nystagmus, head nodding, and abnormal head turn or tilt. Its pathogenesis remains unknown. The onset of the condition is usually between 4 and 12 months of age, and the signs tend to remit within 1 to 2 years of onset, but have been reported to persist for as long as 8 years (Gottlob et al. 1995a). Head nodding is not always present, and often follows the onset of nystagmus. It is usually intermittent and of lower frequency than the nystagmus (Gottlob et al. 1992). The nystagmus is commonly of small amplitude and high frequency (shimmering nystagmus). Both nystagmus and head nodding can occur in any plane (horizontal, vertical, oblique, or torsional). Strabismus and amblyopia may be present, but on the whole, patients are healthy and the diagnosis is made retrospectively, on exclusion of neurological and ophthalmological disease and clinical improvement. It is not considered to be familial, though there have been two reports of spasmus nutans occurring in monozygotic twins (Hoyt and Aicardi 1979, Katzman et al. 1981).

There have been several reports of patients presenting with signs mimicking that of spasmus nutans with asymmetric nystagmus and head nodding, who were subsequently found to have intracranial pathology. Gliomas involving the optic nerves, chiasm, and the third ventricular region are the most common (Schulman et al. 1979, Antony et al. 1980, Albright et al. 1984, Newman et al. 1990). Asymmetric nystagmus has also been reported as the presenting sign of a thalamic lesion (Baram and Tang 1986), of an arachnoid cyst (Spaide et al. 1985), of opsoclonus-myoclonus (Allarakhia and Trobe 1995), and of Leigh’s subsacute necrotizing encephalomyelopathy (Sedwick et al. 1984).

Asymmetric pendular nystagmus which predominantly involves an eye with poor vision may occur secondary to unilateral optic-nerve disease or more rarely in cases with profound amblyopia (Leigh et al. 1989). Monocular nystagmus can also occur after the development of a dense cataract, but often disappears when vision is restored after surgery (Pratt-Johnson and Tillson 1989, Good et al. 1993, Yagasaki et al. 1993).

We set out to investigate the prevalence and diagnosis of patients presenting with asymmetric horizontal nystagmus to the Ophthalmology Department at Great Ormond Street Children’s Hospital, London in order to assess the relative prevalence of serious intracranial pathology.

Method
All patients presenting with nystagmus to the Ophthalmology Department at Great Ormond Street Hospital for Children are routinely referred for flash electroretinogram (ERG), and flash and pattern visual evoked potential (VEP) testing, and...
also for formal assessment of their eye movements. Over an 8-year period (1991 to 1999), 277 children presenting with nystagmus were recorded in the visual electrophysiology unit. We retrospectively reviewed the medical records of all patients presenting with asymmetric horizontal pendular nystagmus. Diagnoses were established by clinical features, neuroimaging investigations, and by visual electrophysiology (VEPs and ERGs).

**VISUAL ELECTROPHYSIOLOGY**

VEPs were recorded using silver–silver chloride EEG electrodes placed in a line across the occipital scalp. A midline electrode was sited at O2 (International 10-20 system, approximately 3 cm above the inion) and lateral electrodes were placed midway between the O2 electrode and the ear (4 to 5 cm, depending on head size). All occipital electrodes were referred to a common frontal electrode at Fz. The flash ERG was recorded from a lower-eyelid electrode also referred to Fz (Kriss 1994). Full-field pattern-reversal VEPs were elicited using a checkerboard presented on a large TV display (subtending 28˚ horizontally by 21˚ vertically at the eye). Five stimulus check sizes ranging from 25 minutes to 400 minutes of arc were used (25, 50, 100, 200, and 400 mins). The laboratory was fully darkened and a Grass PS22 photic stimulator lamp, held 15 cm in front of the eye was used to elicit mixed cone–rod ERGs. Rod-mediated ERGs were elicited using a dim-blue and white flash. Cone-mediated ERGs were elicited using a red flash, and bright white flash and 30Hz flicker under photopic conditions (Kriss and Russell-Eggitt 1992).

**EYE MOVEMENT RECORDING**

Eye movements were recorded using dc-coupled electrooculography (EOG). EEG electrodes were placed on each outer canthus of either eye and the earth electrode was placed in the middle of the forehead. Patients sat on a parent/carer’s lap and the head was held steady by the parent/carer. Video monitoring of the patient was carried out during the recording session (Harris et al. 1992). Optokinetic nystagmus was elicited by rotating a brightly coloured and patterned, full-field curtain around the patient. Leftward and rightward optokinetic nystagmus were recorded at speeds of 25 and 50˚/s. Optokinetic nystagmus status was qualitatively assessed as normal or abnormal (Jacobs et al. 1992).

**Results**

Of the 277 patients presenting with nystagmus, most (223 of 277) had the typical conjugate horizontal nystagmus with the majority (152 of 223) being diagnosed with congenital idiopathic or sensory defect nystagmus (based on visual electrophysiological and clinical findings), and 71 had nystagmus...
secondary to neurological pathology. Thirty patients had vertical nystagmus. Twenty-four had horizontal asymmetric pendular nystagmus. The majority of these patients with asymmetric nystagmus (18 of 24) first presented to the ophthalmologist, and five presented first to the neurologist. The age range of onset of nystagmus was birth to 9 years. One patient with a stormy perinatal period including cardiac problems, had initially been under the care of the paediatricians. The nystagmus was assessed using EOG, and by visual inspection of video recordings.

The patients with asymmetric nystagmus could be divided into three diagnostic categories, based on the results of clinical, electrophysiological, and neuroimaging studies.

SPASMUS NUTANS
Seven patients were placed in this category based on normal clinical, neuroimaging, and visual electrophysiology (VEPs and ERGs) and optokinetic nystagmus findings. In all cases there was a fine, high frequency, pendular horizontal nystagmus, which could be seen superimposed upon the normal optokinetic response (Fig. 1). Head nodding and abnormal head posture, were present in four patients.

All seven patients had presented under 1 year of age, and all were healthy and doing well at follow-up. Acuities were invariably lower in the eye with the greater nystagmus and varied between 6/6 and 6/24. The nystagmus had a tendency to decrease in intensity as the patient got older: the oldest patient was 7 years of age at follow-up, and was found to have minimal end-point nystagmus, although there still remained an interocular difference in Snellen acuities (right eye 6/12, left eye 6/6). Optic disc examinations were normal.

NEUROLOGICAL PATHOLOGY
Twelve patients with asymmetric nystagmus were found to have frank neurological problems. Neuroimaging studies identified chiasmal gliomas in five children; a sixth child had craniopharyngioma and a further two showed delayed myelination. All these children had abnormal pale discs, the exception being the child with a craniopharyngioma whose discs were reported as normal. The flash ERGs were normal in all these cases but the flash and pattern VEPs were degraded (ill-defined, broadened waveform) and attenuated (<6 μV) in all cases, and showed significantly prolonged latencies (>115 ms) in the patients with poor myelination (Fig. 2). The optokinetic nystagmus was well preserved in these patients.

The eighth patient with neurological pathology had been born preterm and had experienced various perinatal complications including septicaemia, necrotizing enterocolitis, and patent ductus arteriosus. MRI showed widespread mild white-matter abnormalities. The flash ERGs were normal and the pattern VEPs were near the lower limit of normal amplitude (6 μV), being somewhat attenuated and consistent with mild postretinal dysfunction. The ninth patient, who presented with seizures, was subsequently diagnosed with infantile Batten disease (neuronal ceroid lipofuscinosis). He was referred to the ophthalmology department because of the presence of asymmetric pendular nystagmus. The flash ERGs and VEPs were found to be significantly attenuated.

![Figure 2: Flash ERGs and flash and checkerboard reversal VEPs from (a) a 3-year-old control participant, (b) a 3-year-old child with delayed myelination, and (c) a 2-year-old child with chiasmal glioma. Flash ERGs are normal in all three children. However, there was prolonged main positive VEP component (down arrows) for flash and pattern VEPs in (b) child with delayed myelination and markedly degraded flash VEP (down arrow), and absent pattern VEPs from (c) child with chiasmal glioma.](https://example.com/figure2)
The optokinetic nystagmus of the last two patients had poor gain.

We have also included in this category two patients who could also be suitably classified in the sensory defect category (below): one patient had bilateral optic nerve hypoplasia, and the other had bilateral optic atrophy. Both patients had normal flash ERGs, but significantly attenuated and degraded flash and pattern VEPs. No abnormalities were noted in MRI.

More than half of the patients in this category presented originally to the ophthalmologist (7 of 12). Of the remaining five, four were secondary referrals from neurologists (one chiasmal glioma, two with poor myelination and developmental delay but without specific diagnoses, one with infantile Batten disease) and one child who had been born preterm with perinatal problems was referred by a paediatrician.

**CONGENITAL SENSORY DEFECT NYSTAGMUS**

This nystagmus is of early onset (in the first few months of life) and is associated with a wide range of congenital sensory pathway abnormalities including albinism, cone dysfunction, cataract, aniridia, and numerous others (Casteels et al. 1992). Five children were diagnosed as having sensory defect nystagmus based on the ERG and VEP findings: three had congenital cone dysfunction (achromatopsia), one had cone–rod dystrophy, and one had albinism. Four of these patients also presented with head shaking and abnormal head posture. The optokinetic nystagmus response was normal in all five patients: this is an unusual finding in patients with sensory defect nystagmus who usually have absent optokinetic response (see Discussion). Three patients underwent neuroimaging studies, which were normal.

Those with cone dysfunction had absent cone-mediated ERGs, but well-preserved, normal sized rod-mediated responses. The pattern VEPs to large checks were significantly degraded, and prolonged beyond the upper-latency limits for our laboratory controls, reflecting poor macular function (Fig. 3). The patient with cone–rod dystrophy had abnormal cone-mediated responses, but also significantly attenuated rod-mediated ERGs.

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**Figure 3:** Flash ERGs to scotopic bright white (mixed cone- and rod-mediated responses), photopic bright white flash (cone-mediated responses), and dim-blue flash (rod-mediated responses) from (a) an age-matched control participant and (b) from a 2-year-old child with congenital cone dysfunction. Note: attenuated ERG and prolonged 'b' wave latency of scotopic white flash ERG in patient 'b' relative to control 'a' patient, indicating that it is predominantly rod generated. Patient 'b' had absent photopic white flash ERGs that are cone mediated but well-preserved rod-mediated ERGs to dim-blue flash. Occipital pattern reversal VEPs using 50 minute checks failed to elicit a recognizable response from patient reflecting poor macular function.
The child with albinism had normal flash ERGs but flash VEPs showed the characteristic occipital crossed asymmetry when comparing the occipital distribution of responses from each eye. This VEP feature is associated with albinism and the excessive decussation of monocular fibres at the chiasm (Russell-Eggitt et al. 1990). Clinical examination demonstrated mild iris transillumination and a blond fundus.

Discussion
This retrospective study has shown that half of patients presenting to our unit with asymmetric or monocular nystagmus had some form of intracranial pathology. The most common being chiasmal glioma, other pathologies included delayed myelination, craniopharyngioma, and optic-nerve hypoplasia. This emphasizes the need for those presenting with asymmetric nystagmus to undergo neuroimaging studies. All our patients had undergone flash and pattern VEP and ERG testing (non-invasive and relatively cheap, and rapid) when they presented to the ophthalmology department at Great Ormond Street Hospital. All had abnormal VEPs and were reported as having ‘postretinal dysfunction’. The rate of false positives for abnormal electrophysiology in our laboratory is low: good compliance with the test procedures is ensured with video monitoring of the child’s fixation and behaviour; recordings are repeated when necessary. This emphasizes that visual electrophysiology can be a valuable first-line of investigation, and can give a reinforcing indication for the need to perform neuroimaging studies.

There have been few systematic studies assessing the eventual diagnosis of children presenting with asymmetric nystagmus. Farmer and Hoyt (1984) found that 6 of 11 children with monocular nystagmus had chiasmal tumours, and four had spasmus nutans, but there were no consistent clinical findings that definitely separated the two groups. A multicenter study by Lavery and coworkers (1984), reported 10 children with chiasmal gliomas who had presented with spasmus nutans-like eye movements. The average time in which the tumour was diagnosed after the onset of nystagmus was 8.6 months, and the most consistent clinical finding in all children was the development of optic atrophy. More recently, a large study investigated over a 6-year period the prevalence of intracranial lesions in 67 consecutive children presenting with asymmetric nystagmus and followed for an average of 3.3 years (Arnoldi and Tychsen 1995). Interestingly, only 43% of these patients had neuroimaging studies, and none of those studied had intracranial gliomas. The more common problems (in 61%) were a history of prematurity, developmental delay, or other systemic problems. The authors concluded that neuroimaging studies might not always be warranted in patients with isolated asymmetric nystagmus. (VEPs and ERGs were not reported in any of the above studies).

In our study visual electrophysiology was valuable in indicating neurological abnormality: flash and pattern VEP recordings showed good sensitivity as they were abnormally altered in both amplitude and latency in all patients with the neurologically acquired nystagmus. Other studies (Lavery et al. 1984, Arnoldi and Tychsen 1995) have reported that optic atrophy is an important sign distinguishing between the benign spasmus-nutans condition and the life-threatening chiasmal gliomas. In our study, all five patients with chiasmal gliomas also had optic disc pallor, however the child with craniopharyngioma was reported as having normal discs.

The presence of optic atrophy usually requires the existence of a compressive lesion of some moderate duration (>6 weeks), and the lack of optic disc pallor does not necessarily imply absent pathology. For example, pattern and flash VEP abnormalities can precede clinical optic disc changes in compressive lesions due to osteopetrosis (Thompson et al. 1998). Visual electrophysiology testing, which is a non-invasive, risk-free test procedure that does not require an anaesthetic, is of great value in investigating persons with suspected compressive lesions (Kriss and Thompson 1997). Furthermore, VEP/ERG testing was also effective in helping to diagnose the significant group of patients with sensory defect asymmetric nystagmus, which included patients with congenital cone dysfunction and/ or albinism. It is only after the exclusion of intracranial lesions and sensory defects that the label of spasmus nutans could be retrospectively assigned to an otherwise healthy child.

There have been two reports of retinal disease presenting with the features of spasmus nutans: Lambert and Newman (1993) and Gottlob and colleagues (1995b) described a total of three patients with congenital stationary night blindness presenting with asymmetric nystagmus and head shaking. However, spasmus nutans features have not been described previously in association with cone dysfunction, albinism, or cone–rod dystrophy. Clinically, it is often difficult to diagnose these conditions in young children, and VEP/ERG testing is very reliable in establishing a diagnosis – over 20% of our patients with asymmetric nystagmus had a sensory defect problem.

Although several authors have listed monocular visual loss as the third cause of monocular or asymmetric nystagmus, in our series none of the patients fell into this category. This is most probably due to patient referral bias for VEP/ERG testing: children with known unilateral disease and horizontal pendular nystagmus in the affected eye are often not investigated with visual electrodiagnostics, particularly as the nystagmus is likely to decrease or disappear after treatment (Good et al. 1993).

This study has shown that optokinetic nystagmus in patients with asymmetric pendular nystagmus is usually well preserved, and considered to be within normal limits. There were two exceptions: one was a child with Batten disease, and the other a child with perinatal complications and white-matter abnormalities. The abnormally degraded optokinetic response in these two individuals could be ascribed to cortical lesions affecting the optokinetic pathways (Harris 1997). It is interesting to note that all persons with spasmus nutans, and those with congenital sensory defect nystagmus, had preserved optokinetic nystagmus with their own pendular nystagmus superimposed upon the optokinetic response. This oculomotor characteristic is seen in those with acquired pendular nystagmus secondary to various neurological conditions such as demyelinating disease (Gresty et al. 1982) and dysmyelination (Harris 1997). Another feature that is shared between our patients and those with acquired pendular nystagmus is that the nystagmus tends to remain pendular in all directions of gaze. These features are not usually associated with typical sensory defect nystagmus which is characterized by a disrupted optokinetic nystagmus response, nystagmus waveform that usually varies with directions of gaze (becoming jerky with accelerating horizontal slow-phases), and often has a null zone in which the nystagmus is minimal or absent.
It has been suggested by Harris (1995) that it could be the nystagmus waveform per se that interacts with optokinetic nystagmus and influences the disruption or preservation of the optokinetic response.

Spasms nutans was the eventual diagnosis in only seven of our patients and such a diagnosis was eventually made after normal clinical, visual electrodiagnostic, and neuroimaging studies. Our findings indicate that half of all patients presenting with asymmetric or monocular nystagmus are likely to have intracranial pathology. Thus, all patients with asymmetric nystagmus should have neuroimaging studies to help identify the lesion. However, visual electrophysiology should also be performed routinely to provide information regarding the functional integrity of the visual pathways as a high proportion of these patients can have abnormalities of the anterior visual pathway. Visual electrodiagnostics (VEPs and ERGs) will reliably identify this significant number of patients with asymmetric nystagmus who have a defect of the sensory visual pathway.

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