

Nystagmus characteristics in congenital stationary night blindness (CSNB)

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ABSTRACT

Aim: To analyse nystagmus characteristics in patients with congenital stationary night blindness (CSNB) for differentiation from other forms of early childhood nystagmus.

Methods: Horizontal and vertical eye movements of 10 patients (6–46 years, mean 17.1 years, median 12.5 years) with CSNB (eight with CSNB1, two with CSNB2) were recorded with the scleral magnetic search coil technique or by electro-oculography. Nystagmus characteristics such as the amplitude, frequency, conjugacy and intermittency were analysed.

Results: All patients had continuous, pendular, oblique and mostly dysconjugate nystagmus of high frequency and low amplitude. In seven cases, a large horizontal or vertical jerk nystagmus with increasing, decreasing or constant velocity was superimposed. Jerk nystagmus was mostly intermittent and conjugate. Head nodding was found not to be compensatory.

Conclusions: Eye-movement recordings of CSNB patients disclosed specific nystagmus characteristics, such as an oblique direction, superimposed waveforms and dysconjugate eye movements. These features may help to distinct nystagmus in CSNB from other forms of early infancy nystagmus, such as congenital idiopathic nystagmus, latent nystagmus and spasmus nutans. We found nystagmus in CSNB to be similar to the nystagmus reported in blue-cone monochromatism and rod monochromatism, and in patients with a severe sensory defect. The nystagmus characteristics described should prompt electroretinographic investigation in cases of uncertain diagnosis.

Nystagmus in early childhood often represents a benign disorder such as congenital idiopathic nystagmus (CIN), latent nystagmus or spasmus nutans. However, nystagmus can also be the first sign of a brain tumour,¹ a hereditary retinal disorder² or poor vision.³ Waveforms have been studied extensively in idiopathic nystagmus,^{4,5} spasmus nutans⁶ and rod and blue-cone monochromatism.^{2,7} Twenty to 40% of the patients with congenital stationary night blindness (CSNB) were found to present with nystagmus.^{8,9} The nystagmus waveform in CSNB has rarely been described,^{10,11} and we do not know whether specific characteristics exist, which would allow distinction from other entities in order to prompt necessary electrophysiological work-up and genetic counselling without delay. CSNB is caused by mutations in genes encoding either components of the phototransduction cascade or proteins presumably involved in signalling from photoreceptors to adjacent second-order neurons. CSNB1 (complete type) was found to result from mutations of the

NYX gene (nyctalopin gene) leading to a complete defect of the ON-bipolar cells or their synapses in the rod and cone visual pathways.¹² X linked recessive CSNB2 (incomplete type) results from mutations in the calcium channel (CACNA1F) gene, which encodes the retina specific alpha 1-subunit.¹³ Alterations induce severe changes in channel activity leading to an incomplete defect of the ON and OFF bipolar cells or their synapses in the rod and cone visual pathways.¹⁴ Both, CSNB1 and 2 show a negative electroretinogram (ERG) with a decreased b-wave in the scotopic as well as the photopic ERG.¹⁵ Rod function is most severely affected in CSNB1. There is also a substantially reduced cone a-wave, and a reduced 30 Hz flicker ERG response in CSNB2.¹⁶ The aim of this study was to characterise the nystagmus in patients with CSNB using quantitative eye-movement recordings and to investigate whether differentiation from other nystagmus forms of early childhood is possible.

PATIENTS

The study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of St. Gallen/Switzerland. All patients or the patients' parents gave informed consent to participate in the study. We studied 10 patients (6–46 years, mean 17.1 years, median 12.5 years) with CSNB, two of them having had CSNB1 and eight CSNB2. A complete ophthalmological examination was performed on one or more occasions. None of the patients had undergone genetic testing.

METHODS

Eye movements were recorded with the electro-magnetic search coil technique in the three adults (patients 7, 8 and 9). An induction coil, mounted in a scleral contact lens, was placed on the limbus. The patient sat within a frame which generated an alternating (20 kHz) horizontal and vertical magnetic field around the head and consequently induced an alternating voltage in the ocular coil. An electronic control module (Skalar) amplified and demodulated the voltage, which was induced in the scleral search coil. After amplification and phase-locked detection, two analogue voltages were obtained which were proportional to the sine of the horizontal and vertical eye deviation. A chin- and headrest facilitated the fixation of the subject's head. Since the application of scleral contact lenses in children is difficult, we recorded their eye movements using electro-oculography (EOG) and provide the obtained data as supportive evidence. A Vision Monitor System (Metrovision, Villeneuve d'Ascq, France) was used. Stat-Trace II (Niko Med

USA, New Brunswick, NJ) electrocardiographic electrodes were placed nasally to the medial canthi, temporally to the lateral canthi, above the upper eyelids and underneath the lower lashes. The indifferent electrode was positioned centrally above the glabella. Signals were DC-amplified ($\times 6000$) and filtered (DC bandpass, 76 Hz). Eye position was recorded on a digital computer with a sampling rate of 230 Hz. Data were converted from analogue to digital with 12 bits. For calibration, a red laser target was back-projected on a screen at 150 cm and used for smooth pursuit and saccadic eye-movement stimulation within 20° to the right, left, up and down. In addition, subjects were examined during fixation in primary and in 20° horizontal and vertical gaze. Eye-movement recordings were obtained during binocular and monocular viewing. Analysis of the recordings included nystagmus waveform, amplitude, frequency, conjugacy and direction.

RESULTS

Clinical examination

The data from the most recent exam are listed in table 1. Visual acuity in our patients ranged from 0.1 to 0.9 independent of the CSNB type. This corresponds to previous data with visual acuities ranging from 0.1 to 1.0 in both types of CSNB, with a mean of 0.4–0.5.⁸ CSNB1 can be associated with high or moderate myopic refractive errors, while CSNB2 patients were found to have mild myopic or hyperopic refractive errors.⁸ Consistent with the literature, the two patients with CSNB1 were myopic. Out of the CSNB2 group, one patient was hyperopic, and seven were myopic. None of them complained about oscillopsia, but they all suffered from discrete to pronounced reduction in scotopic vision. Dark adaptation threshold was increased in patients 1–9 but was not tested in patient 10. The ERG of patients 1–7 and 9 (CSNB2) showed a smaller b- than a-wave of the rod and cone-response (negative ERG). The rod function was decreased to below 50% of the norm. The amplitude of the cone-response was reduced to 20–40% of the norm value. In patients 8 and 10 (CSNB1) rod

activity was almost extinguished. The cone response was negative with a normal a-wave.

Eye-movement recordings

Patients 1, 4, 5, 6, 7, 8, 9 and 10 had first been diagnosed as having congenital idiopathic nystagmus. They presented clinically with pendular and jerk, horizontal, vertical or rotatory nystagmus. In patients 5, 9 and 10, nystagmus dampened in their preferred head position.

Two half brothers (patients 2 and 3) had fine pendular nystagmus, head nodding and head tilt, and had first been diagnosed as having spasmus nutans. MRI and neuropaediatric examination were normal. Nystagmus in the older brother decreased with time and disappeared clinically, so the diagnosis of spasmus nutans seemed to be confirmed. Visual acuity improved from 0.3 to 0.7 in his right eye and from 0.4 to 0.9 in his left eye until the age of 11. The younger brother showed similar spasmus nutans-like eye movements. However, nystagmus intensity, head nodding and abnormal head position did not change with age, and visual acuity was only 0.2 in his right eye and 0.3 in his left eye. This prompted us to obtain an ERG of both brothers, which led to the diagnosis of CSNB. Each patient's eye-movement characteristics are listed in table 2.

All of them displayed a continuous oblique pendular nystagmus independent of the CSNB type. During fixation, it was of a high frequency, between 10 and 20 Hz, and of a low amplitude, between 1 and 4° (fig 1). During smooth pursuit, slightly lower frequencies (3–8 Hz) and higher amplitudes of up to 8° were detected (fig 2). In all patients, pendular oscillations were dysconjugate most of the time. In eight of the 10 patients, independently of the type of CSNB, a jerk nystagmus of increasing, constant or decreasing velocity was superimposed on the pendular nystagmus (fig 3). In comparison with the pendular nystagmus, it was intermittent in all cases except for one and mostly conjugate. Jerk nystagmus was slower with a frequency of 2–4 Hz, and the amplitude ranged from 2 to 15° . In nine patients, the direction of the nystagmus

Table 1 Data from the most recent exam

Patient	Sex	Age	Type of CSNB	Refraction (retinoscopy)		Visual acuity at last examination		Colour defects (Panel-D-15)	
				OD	OS	OD	OS		
1	M	9	CSNB2	–9.0sph –2.0/30°		0.1		Intermittent exotropia	Blue
				9.25sph –1.5/150°		0.2			
2	M	9	CSNB2	–2.25sph –1.0/40°		0.2		Intermittent exotropia	Blue
				–2.75sph –1.0/150°		0.3			
3 (half brother of 2)	M	11	CSNB2	–0.75/55°		0.7		Orthotropia none	None
				–0.75/178°		0.9			
4	M	9	CSNB2	–0.75/180°		0.3		Alternating esotropia	None
				–0.25sph		0.1			
5 (brother of 4)	M	14	CSNB2	–1.5sph –2.0/42°		0.3		Orthotropia	None
				+0.5sph –2.0/151°		0.4			
6	F	17	CSNB2	+5.0sph		0.16		Alternating esotropia	Blue
				+6.0sph –1.0/0°		0.16			
7 (sister of 6)	F	21	CSNB2	–1.75sph –1.5/0°		0.08		Orthotropia	Blue
				–2.25sph –1.75/10°		0.08			
8	M	46	CSNB1	–2.5sph –1.25/110°		0.6		Intermittent exotropia	Red, green
				–3.0sph –0.75/60°		0.7			
9	M	29	CSNB2	+1.5sph –6.5/0°		0.1		Left exotropia	Blue
				+1.5sph –6.5/0°		0.1			
10	M	6	CSNB1	–1.75sph –0.75/75°		0.2		Right esotropia	Not obtained
				–1.0sph –0.5/75°		0.2			

Table 2 Patients' eye-movement characteristics

Patient	Pendular nystagmus during fixation			Jerk nystagmus during fixation					Head position
	Frequency	Amplitude	Conjugacy right eye/left eye	Velocity	Amplitude	Frequency	Direction	Intermittency	
1	16–18 Hz	1–4°	Mostly dysconjugate	Increasing and decreasing	5°	4 Hz	Horizontal	Intermittent	Down
2	10–18 Hz	2–8°	Mostly dysconjugate	Increasing, constant, decreasing	8–10°	4 Hz	Vertical	Intermittent	Down and head nodding
3	10–16 Hz	1–4°	Dysconjugate	None	None	None	None	None	Left
4	14–16 Hz	2–4°	Dysconjugate	Increasing and decreasing	10–12°	2–4 Hz	Oblique	Intermittent	Down
5	13–16 Hz	2–4°	Mostly dysconjugate	None	None	None	None	None	Left
6	12–14 Hz	2–4°	Mostly dysconjugate	Decreasing	3–5°	2–4 Hz	Vertical	Intermittent	None
7	10 Hz	0.5–1°	Mostly dysconjugate	Decreasing	2–4°	2–3 Hz	Oblique	Continuous	None
8	14 Hz	2–4°	Mostly dysconjugate	None	None	None	None	None	None
9	18–20 Hz	2–4°	Mostly dysconjugate	Decreasing	8–10°	2 Hz	Oblique	Intermittent	None
10	14–18 Hz	1–4°	Mostly dysconjugate	Decreasing	4–8°	2 Hz	Oblique	Intermittent	Left

did not change depending on the fixating eye. In patient 6, the direction of the fast phase changed during the cover test and revealed a latent nystagmus.

Patient 2 presented clinically with head nodding and a preferred head down position. Fixating the target with his head straight and without head nodding, a small, oblique pendular nystagmus was seen. Superimposed was a large amplitude upbeat nystagmus with either increasing or constant velocity of the slow phase (fig 4A). Recordings in his preferred head position showed a pendular nystagmus of slightly lower amplitude. Vertical jerk nystagmus was no longer observed (fig 4B). When the patient fixated in his preferred head position but this time with head nodding, nystagmus was the same as without head nodding (fig 4C).

Follow-up of the patients did not reveal clinical changes or a change in nystagmus, except for patient 3, who showed an increase in visual acuity and dampening of nystagmus with decreasing frequency and amplitude.

DISCUSSION

Eye-movement recordings in CSNB patients revealed specific nystagmus characteristics. We found a dysconjugate pendular nystagmus of small amplitude, high frequency and an oblique direction. Taking the relatively small sample size into account,

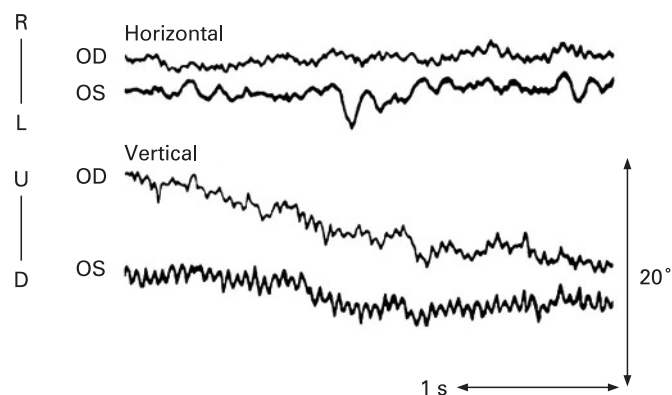


Figure 1 Search coil recordings of patient 8 during fixation. Pendular nystagmus of high frequency and small amplitude with an oblique (horizontal and vertical components) direction are displayed on the horizontal and the vertical traces of both eyes. Oscillations are dysconjugate most of the time.

in most patients the pendular nystagmus was superimposed on a jerk nystagmus. Its slow phase was of increasing, constant or decreasing velocity, and it was mostly conjugate. While head nodding did not influence the nystagmus, preferred head positioning decreased the amplitude of the pendular nystagmus and extinguished the jerk nystagmus. Clinical follow-up of patient 3 showed an increase in visual acuity and a significant decrease in nystagmus frequency and amplitude. Interestingly, the patients who presented with a pure pendular nystagmus (patients 3, 5, 8) were those with the highest visual acuity (up to 0.9). A possible correlation is supported by the results of patient 2, whose jerk nystagmus was suppressed in his preferred head position.

The detection of these characteristic features is facilitated by eye-movement recordings, but some of them can be revealed during clinical examination.

The nystagmus in our patients can be distinguished from CIN in several ways. Nystagmus direction was mainly oblique, whereas CIN is predominantly horizontal. The majority of our patients showed superimposed larger waveforms, whereas superimposed components are not typical of CIN.⁵ Congenital idiopathic jerk nystagmus usually presents with a slow phase of increasing velocity in comparison with the constant, increasing or decreasing velocity of our patients' jerk nystagmus. Further, one of the main features of CIN is the conjugacy of eye movements. Only one study described dysconjugacy in two of 25 children with CIN.⁶ Pendular nystagmus in all of our patients was dysconjugate. Since some of the characteristics such as the nystagmus velocity are difficult to judge by observation without eye-movement recordings, sometimes patients with CSNB may be misdiagnosed as patients with CIN. Therefore, in all patients with suspected CIN, especially in those with reduced visual acuity, an ERG should be performed once throughout the diagnostic work-up.

Spasmus nutans (SN) patients show several features similar to those of nystagmus in CSNB.¹⁰ Pendular nystagmus with high frequencies of up to 15 Hz and low amplitudes between 0.5 and 3° was demonstrated in SN eye-movement recordings.¹⁷ Also, eye movements are dysconjugate most of the time. Similarities in the clinical long-term follow-up with an increase in visual acuity and a decrease in nystagmus intensity can make differential diagnosis difficult. However, differentiation is possible by the influence of head nodding on the eye movements. In SN, the fine, fast and dissociated nystagmus changes to larger and slower symmetric eye movements during head

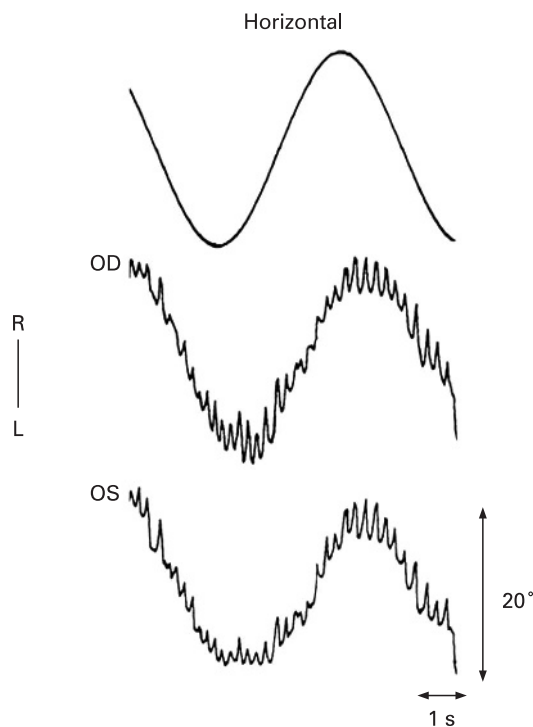


Figure 2 EOG recordings of patient 1 showing horizontal smooth pursuit eye movements. The horizontal traces of both eyes reveal pendular, mostly conjugate nystagmus of up to 8° .

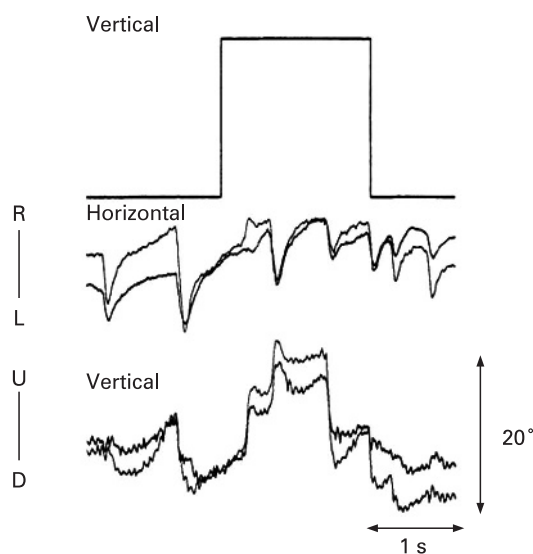


Figure 3 EOG recordings of vertical saccades of patient 10. The horizontal and vertical traces present a small pendular nystagmus with horizontal and vertical components (oblique), which is superimposed on a larger horizontal jerk nystagmus with decreasing velocity.

nodding, which correspond to a normal compensatory vestibulo-ocular reflex.¹⁸ In contrast, head nodding was not found to be compensatory in our patients, similar to other reports of nystagmus in retinal disease.¹¹

Latent nystagmus typically has a jerk waveform with decreasing slow phase velocity. It changes direction depending on the fixating eye and can increase in amplitude during occlusion.¹⁹ Some of our CSNB patients presented with a jerk nystagmus of decreasing velocity. However, in all but one, the

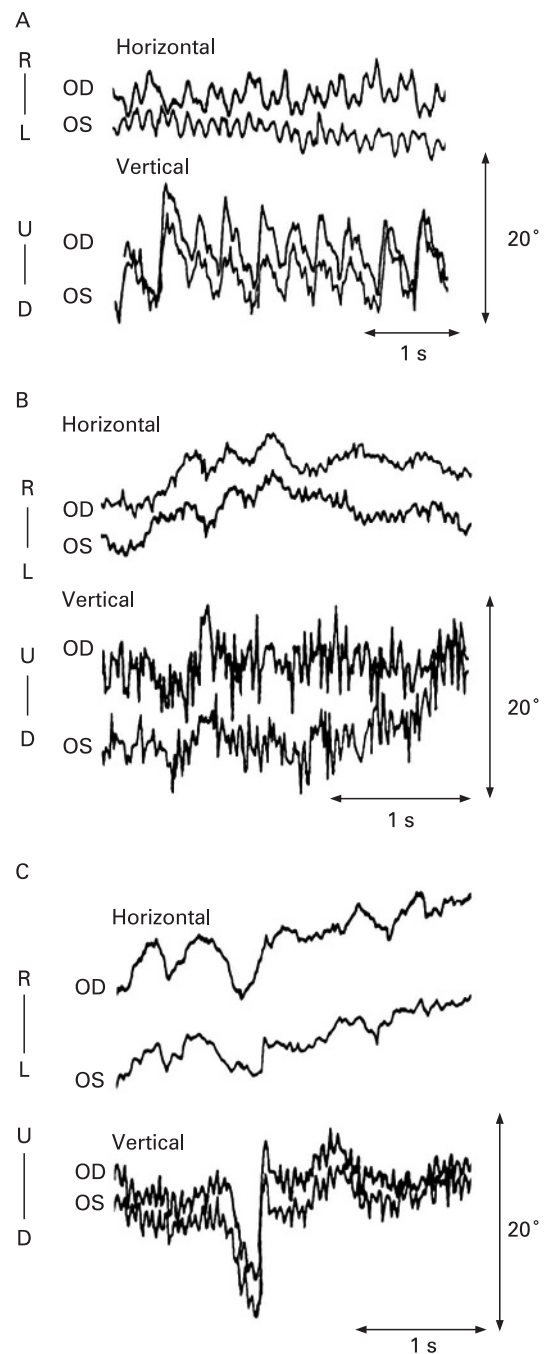


Figure 4 EOG recordings of patient 2, who had a preferred head position and head-nodding, during fixation of a target straight ahead. (A) In a straight head position and no head nodding, horizontal and vertical traces of both eyes display a small pendular nystagmus with horizontal and vertical components, indicating an oblique direction. The vertical traces show an additional conjugate large amplitude upbeat nystagmus with mainly constant velocity of the slow phase. (B) In the patient's preferred head position (upgaze) but without head nodding, the horizontal and vertical traces of both eyes display only pendular nystagmus. (C) In the patient's preferred head position (upgaze) and with head nodding, the horizontal and vertical traces of both eyes present pendular nystagmus of similar amplitude and frequency as recorded without head nodding.

cover test did not reveal a change in nystagmus direction, which makes distinction from latent nystagmus possible.

Differentiation from nystagmus in rod monochromatism (RM) and blue cone monochromatism (BCM) is difficult.

Clinically, these patients usually present with a higher degree of photophobia and colour blindness.²⁰ Both groups can have a pendular nystagmus of low amplitude and high frequency which is mainly dysconjugate. Also, head nodding can be found in both patient groups. In contrast to the CSNB patients of our study, nystagmus in RM and BCM is either jerk or pendular; it usually does not have superimposed waveforms.⁷ The overlapping nystagmus characteristics in these retinal entities indicate the differential diagnostic importance of an electrophysiological work-up and genetic analysis in the search for mutations in the *NYX* or the *CACNA1F* genes, or the *CABP4* gene, a member of the calcium-binding protein family, which was recently found to lead to CSNB2 as well.²¹

Eye-movement recordings in children with a severe sensory defect due to congenital affections such as optic-nerve hypoplasia or bilateral congenital cataract can reveal similar or identical nystagmus characteristics, as we found in CSNB. Small pendular nystagmus with frequencies up to 14 Hz and large superimposed jerk nystagmus waveforms were discovered.³ Different to the CSNB patients of our study, small jerk nystagmus superimposed on larger pendular nystagmus has also been described. Since congenital optic nerve affections may present with nystagmus features indistinguishable from congenital retinal conditions, one must be aware of the possibility of masking a retinal dystrophy in case of visual loss, pale discs and normal appearing fundi.

CONCLUSION

We describe for the first time specific nystagmus characteristics in CSNB. Typically, patients presented with dysconjugate pendular nystagmus of small amplitude and high frequency, on which a large jerk nystagmus with decreasing, increasing or constant velocity was often superimposed. These characteristics help to differentiate from congenital idiopathic nystagmus, latent nystagmus and spasmus nutans. A similar or even the same pattern can be found in children with RM, BCM or severe visual impairment. Therefore, in cases of the described, atypical nystagmus features and unclear diagnosis, an electrophysiological work-up should be prompted.

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Competing interests: None.

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