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Ocular vestibular evoked myogenic potentials are abnormal in internuclear ophthalmoplegia

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ABSTRACT

Objective: The cervical vestibular evoked myogenic potential (cVEMP) is sensitive to lower brainstem lesions affecting the vestibulo-collic pathway. We wished to determine whether the ocular VEMP (oVEMP), a recently-described otolith–ocular reflex, is also abnormal in patients with brainstem lesions. We tested patients with internuclear ophthalmoplegia (INO), caused by a brainstem lesion in the medial longitudinal fasciculus (MLF), to investigate whether the oVEMP is abnormal in patients with a lesion of the otolith–ocular pathway.

Methods: We describe a patient who developed a right INO during his first episode of demyelination, and report results from 12 additional patients, most of whom had multiple sclerosis. All subjects were stimulated with air-conducted tone bursts. cVEMPs and oVEMPs were measured using surface electrodes placed over the neck and beneath the eyes.

Results: Overall, oVEMPs showed significantly more abnormalities (69%) than cVEMPs (8%). Ocular VEMPs were absent with stimulation of 13/26 ears, significantly delayed in 5/26 cases and normal in only 8/26 cases.

Conclusion: Ocular VEMPs are often abnormal in patients with multiple sclerosis who have an INO, while cVEMPs are usually normal.

Significance: Ocular VEMPs provide a new, non-invasive method for examining central vestibular pathways in humans and are sensitive to lesions of the MLF.

1. Introduction

A novel method for testing otolith–ocular pathways in humans is the ocular vestibular evoked myogenic potential (oVEMP), a short-latency reflex recorded from the extraocular muscles prior to an evoked eye movement (Todd et al., 2007; for review see Rosengren et al., 2010). Similar to the VEMP recorded from the neck muscles (cervical VEMP/cVEMP), oVEMPs are evoked by vestibular stimuli such as loud sound and vibration and are the earliest manifestation of the vestibulo-ocular reflex (VOR). They are primarily measured from the extraocular muscles of the eye contralateral to the stimulus, i.e. the pathway is predominantly crossed (Iwasaki et al., 2007). Ocular VEMPs are typically recorded from surface electrodes placed beneath the eyes and are thought to originate principally in the inferior oblique muscle (Govender et al., 2009). As loud sounds selectively activate otolith afferents (Murofushi and Curthoys, 1997), the sound-evoked oVEMP is a test of otolith–ocular function. The oVEMP should therefore be abnormal in patients with lesions involving otolith–ocular brainstem pathways above the vestibular nucleus, while the cVEMP, whose projection descends after exiting the vestibular nucleus, should be normal.

A lesion of the brainstem in the medial longitudinal fasciculus (MLF) between the abducens and oculomotor nuclei typically causes an internuclear ophthalmoplegia (INO), a disturbance of conjugate horizontal gaze due to failure of adduction of the eye ipsilateral to the lesion (Leigh and Zee, 2006). As otolith–ocular pathways also travel in or near the MLF, they are often affected in patients with INO (Zwergal et al., 2008). This has been demonstrated by studies of the ocular tilt reaction (OTR), which manifests as ocular torsion, skew deviation and shift of subjective of visual vertical (Westheimer and Blair, 1975). The OTR is a natural response to tilt of the head in normal humans but occurs spontaneously after disruption to otolith–ocular pathways. Brainstem lesions caudal to the pons produce an ipsiversive OTR (torsion of the eyes towards the lesioned side), similar to that evoked by peripheral vestibular dysfunction (Dieterich and Brandt, 1992). In contrast, lesions of the MLF in the pons and mesencephalon (i.e. between the abducens and oculomotor nuclei) produce contraversive OTR (Dieterich and Brandt, 1993; Zwergal et al., 2008). This suggests that otolith–ocular

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fibres in humans course through or near the contralateral MLF and that the pathway crosses the midline between the vestibular and abducens nuclei (Zwergal et al., 2008).

We wished to test whether patients with brainstem lesions above the level of the vestibular nucleus have high rates of ocular VEMP abnormality. We therefore recorded oVEMPs in patients with multiple sclerosis (MS) who had unilateral or bilateral INO. The cVEMP has previously been shown to be sensitive to brainstem lesions involving the vestibulo-collic pathway (e.g. Bandini et al., 2004; Murofushi et al., 2001; Patkó et al., 2007; Sartucci and Logi, 2002; Shimizu et al., 2000; Versino et al., 2002). We therefore compared oVEMPs to cVEMPs recorded with the same stimulus in each patient. As the patients were selected to have a clinical sign of MLF abnormality potentially involving the vestibulo-ocular pathway, but not the vestibulo-collic pathway, we expected higher rates of oVEMP abnormality. We describe an index patient who developed an INO during his first episode of demyelination, and report results from 12 additional patients.

2. Methods

2.1. Case description

A 16 year old male presented with a 2 week history of blurred vision, right facial numbness and loss of taste on the right side of the tongue (patient 1, Table 1). Neurological examination showed a right INO but no other signs. An MRI performed at examination showed multiple T2-weighted signal hyperintensities, consistent with demyelination, though no brainstem abnormality was detected. Visual evoked potentials were well-formed but delayed on the left. The patient underwent VEMP testing 2 weeks after his first presentation. Six weeks later his symptoms had resolved. An MRI performed 8 months afterwards showed new white matter lesions, one of which enhanced with gadolinium, and was accompanied by additional symptoms, leading to a diagnosis of MS.

2.2. Additional patients

Twelve additional patients with INO were tested (4 unilateral, 8 bilateral; Table 1). Eleven had MS and were referred by a specialist MS clinic, while one had an isolated INO due to a presumed vascular lesion (patient 3). The INO was always confirmed by a staff neurologist at the time of testing. The severity of INO and concurrent symptoms varied between the patients. In cases of slowing, rather than failure, of adduction, the INO was termed 'kinetic'. Magnetic resonance images were not generally available. Written informed consent was obtained from all subjects and the study was approved by the local ethics committee.

2.3. VEMP testing

Stimuli were 500 Hz, 2 ms air-conducted tones of 136 to 142 dB peak SPL. Cervical VEMPs were recorded from the ipsilateral sternocleidomastoid muscles using standard recording procedures (Rosengren et al., 2009). Subjects reclined to approximately 30 deg above the horizontal and surface potentials were recorded using pairs of Ag/AgCl electrodes. The active (inverting) electrode was placed over the middle of the sternocleidomastoid muscle (SCM) belly and the reference (non-inverting) electrode over the medial clavicle. An earth was placed on the sternum. Rectified EMG was monitored online and recorded, and care was taken to ensure constant background activation of the SCM between trials. Latency was measured at the p13 peak and amplitudes measured at the p13/n23 response peaks and expressed as a ratio of background muscle activity. To determine cVEMP threshold, intensity was reduced in 6 dB steps over successive trials.

Ocular VEMPs were recorded from electrode pairs placed inferior to the eyes using previously reported techniques (Govender et al., 2009). Recording electrodes were positioned directly below the eyes, with reference electrodes placed 2–3 cm below them on the cheek. An earth electrode was placed near the suprasternal notch. All patients were tested while seated upright. Most patients were tested during maximal up-gaze, however if patients had nystagmus on up-gaze oVEMPs were recorded during neutral gaze (patients 3, 11 and 10). Amplitudes and latencies were measured from the contralateral electrode at the first negative peak (n10). Where two trials were recorded the average value was reported.

To assess latency, patients were compared to a group of 61 normal subjects aged 18–80 yrs (Rosengren et al., unpublished observations). The normal range (mean ± 2 SD) for cVEMP latencies was

Table 1
Clinical characteristics and test results of patients with internuclear ophthalmoplegia.

					cVEMPs						oVEMPs			
					Right stimulation			Left stimulation			Right stimulation		Left stimulation	
Patient	Presentation	Age	Gender	Disease duration	Response	Latency (ms)	Threshold (dB peak SPL)	Response	Latency (ms)	Threshold (dB peak SPL)	Response	Latency (ms)	Response	Latency (ms)
Unilateral INO														
1	R INO	16	M	2 weeks	P	14.6	124	P	17.4	124	P	8.8	A	
2	R kinetic INO	46	F	13 yrs	P	13.8	124	P	16.6	118	P	10.9	P	10.6
3	R kinetic INO	60	M	6 weeks	P	15.6	130	P	15.2	130	P/delayed	13.1	P/delayed	12.3
4	R kinetic INO	39	M	1 week	P	14.2	130	P	14.6	130	P	9.6	P	9.7
5	L INO	27	M	~5 yrs	P	15.0	112	P	18.6	124	A		A	
Bilateral INO														
6	B INO	66	F	~18 yrs	P	17.6	130	A			A		A	
7	B kinetic INO	45	F	5 yrs	P	13.4	124	P	13.6	136	P	11.0	P/delayed*	12.0
8	B INO	57	F	39 yrs	P	17.6	130	P/delayed	20.2	130	A		A	
9	B INO	39	F	17 yrs	P	13.4	124	P	18.4	124	A		A	
10	B INO	46	M	5 yrs	P	15.8	133	P	15.4	124	P/delayed	12.5	A	
11	B INO (worse R)	49	M	~12 yrs	P	15.2	130	P	15.5	130	A		A	
12	B INO (worse L)	47	F	6 yrs	P	14.2	136	P	14.6	118	A		P	11.6
13	B INO (worse L)	53	M	12 yrs	P	15.8	118	P	15.2	118	P/delayed	12.2	P	10.5

Abbreviations: R, right; L, left; B, bilateral; MS, multiple sclerosis; F, female; M, male; INO, internuclear ophthalmoplegia; P, present; A, absent. The side of INO was determined by the side of failure of adduction. *In patient 7, the oVEMP evoked by left stimulation was within normal latency limits on one trial and delayed on the second run, giving a mean latency of 12 ms.