

Vestibular-evoked myogenic potentials in central vestibular disorders

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Abstract Vestibular-evoked myogenic potentials (VEMPs) are short latency manifestations of vestibulo-ocular and vestibulocollic reflexes that originate from the utricle and saccule. Although cervical and ocular VEMPs have mostly been applied to peripheral vestibular disorders, the characteristics and the diagnostic values of VEMPs have been expanded to assess the function of the central otolithic pathways. In the central nervous system, the cervical VEMPs (cVEMPs) are mediated by the vestibular nuclei and uncrossed medial vestibulospinal tract descending in the lower brainstem and spinal cord. In contrast, the ocular VEMPs (oVEMPs) reflect the function of the vestibular nuclei and the crossed vestibulo-ocular reflex (VOR) pathways, mostly contained in the medial longitudinal fasciculus (MLF). Therefore, lesions involving the vestibular nuclei can present abnormalities of both cVEMPs and oVEMPs. The medullary lesions involving the descending MLF or the spinal accessory nucleus impair cVEMPs. In contrast, the lesions involving the MLF, the crossed ventral tegmental tract, oculomotor nuclei and the interstitial nucleus of Cajal can impair oVEMPs. Patients

with unilateral cerebellar infarctions may show abnormal VEMPs especially when they have the ocular tilt reaction. Delayed responses of VEMPs are characteristic of multiple sclerosis (MS). Reduced VEMP responses can be observed in patients with vestibular migraine. VEMPs are useful in evaluating central as well as peripheral otolithic function that are not readily defined by conventional vestibular function tests, and can aid in detecting and localizing central lesions, especially silent brainstem lesions such as tiny infarctions or MS plaques.

Keywords Vestibular-evoked myogenic potentials (VEMPs) · Ocular VEMPs (oVEMPs) · Cervical VEMPs (cVEMPs) · Vertigo · Stroke · Otoliths · Brainstem · Internuclear ophthalmoplegia (INO) · Medial longitudinal fasciculus (MLF) · Multiple sclerosis (MS) · Vestibular migraine

Introduction

Vestibular-evoked myogenic potentials (VEMPs) are now widely used to assess the function of otolithic pathways [1–3]. Cervical VEMPs (cVEMPs) are a manifestation of the vestibulocollic reflex (VCR) and involve measuring the electromyographic (EMG) activity from the tonically activated sternocleidomastoid (SCM) muscles in response to saccular stimulation [2]. VEMPs can also be recorded from the extraocular muscles using the surface electrodes placed over the inferior oblique and inferior rectus muscles, and is termed ocular VEMPs (oVEMPs) [4]. In contrary to the cVEMPs which are an uncrossed inhibitory vestibulospinal response, the oVEMPs represent a crossed excitatory vestibulo-ocular reflex (VOR) (Fig. 1) [5–7]. The VOR is mediated by the vestibular end organ receptors, the

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neurons in the vestibular nuclei, and the ocular motoneurons. Pathways carrying these signals mostly run in the MLF in the upper medulla and pons, but also in other ascending otolithic pathways such as the central ventral tegmental tract, ascending tract of Deiters and the ipsilateral vestibulo-thalamic tract from the vestibular nuclei to the upper brainstem and thalamus [5, 8].

VEMPs have generally been regarded the tests for evaluating the function of the otolithic end organs and their afferents. Thus, those have mostly been applied to the disorders involving the peripheral vestibular system. However, VEMPs also can assess the function of central vestibulospinal and vestibulo-ocular pathways that include the vestibular fascicle and nuclei, the medial vestibulospinal tract (VST), and the medial longitudinal fasciculus (MLF). In addition, the cerebellum may affect VEMP responses by participating in the modulation of the otolithic signals. Therefore, due to possible damage to the vestibular fascicles, vestibular nuclei and their efferents, and cerebellum that are all involved in relaying and processing of the vestibular signals, central vestibular lesions may impair the VEMP responses along the descending (cVEMPs) and ascending (oVEMPs) tracts in the brainstem. Since the vestibulocollic (vestibulospinal) and VOR pathways diverge beyond the nerve root entry zone and the vestibular nuclei, both cVEMPs and oVEMPs would provide valuable information in localizing the central lesions when combined. Thus, a central lesion causing abnormal responses for both cervical and ocular VEMPs is likely to be localized to the vestibular nerve root entry zone or the vestibular nuclei [9, 10]. The cortical representation of saccular stimulation using cVEMPs involves the multisensory cortical network within both hemispheres including the posterior insular cortex, the middle and superior temporal gyri, and the inferior parietal cortex [11, 12].

In this review, we present an overview of basic peripheral physiology and cervical and ocular VEMP abnormalities in central vestibular disorders, and suggest the localizing and diagnostic value of VEMP testing in various central vestibular disorders.

Neural connections of the utricle and saccule

The semicircular canals sense angular acceleration of the head, whereas the otolith organs sense its linear acceleration. The otolith organ consists of two receptors: the saccular and utricular maculae, which are sensitive to vertical and horizontal linear acceleration, respectively. Both the utricular and saccular afferents reach the target neurons in the vestibular nuclei of the brainstem [12, 13]. Even though these otolithic projections are superimposed on each other, the saccular projections are mainly toward the lateral,

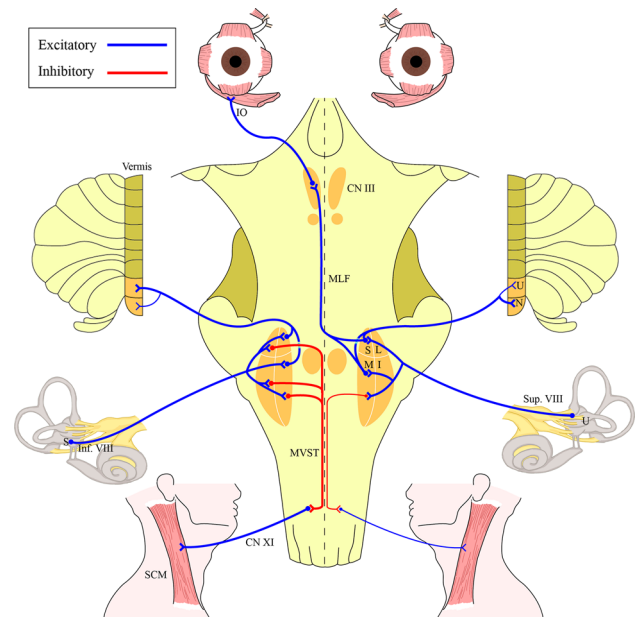


Fig. 1 Schematic illustration of the anatomic pathways involved in the generation of ocular and cervical vestibular-evoked myogenic potentials (VEMPs). Cervical VEMPs are the result of inhibitory postsynaptic potentials on the ipsilateral SCM motoneurons and are mediated by the descending medial vestibulospinal tract (VST) within the medial longitudinal fasciculus (MLF). And, the MLF from the upper medulla to the midbrain is the main pathway of the crossed otolith-ocular reflex responsible for ocular VEMPs. The utricular projections for the vestibulo-ocular function are directed more to the superior and medial nuclei while the saccular projections for the vestibulospinal function are more to the spinal and the lateral vestibular nuclei [12]. The mossy fiber arising from the superior and medial vestibular nuclei mediates projections from the utricle and saccule to the ipsilateral uvula and nodulus [12]. Regarding cVEMPs, saccular stimulation induces inhibitory potentials in the ipsilateral SCM while utricular stimulation evokes ipsilateral inhibitory and contralateral excitatory potentials [16]. However, the utricular contribution to the ipsilateral cVEMP responses has been assumed to be negligible (thin line). For oVEMPs, stimulation of the utricular nerve gives rise to strong activation of the ipsilateral superior oblique and contralateral inferior oblique muscles [14]. Saccular nerve stimulation, in contrast, produces no activation in the majority of extraocular motor neurons. *CN III* oculomotor nucleus, *CN XI* accessory nerve, *F* flocculus, *MLF* medial longitudinal fasciculus, *MVST* medial VST, *Inf. VIII* inferior division of the vestibular nerve, *Sup. VIII* superior division of the vestibular nerve, *VN* vestibular nuclei, *S* saccular macula, *SCM* sternocleidomastoids, *U* utricular macula or uvular in cerebellum, *V* vermis. (Blue line excitatory, red line inhibitory)

particularly the spinal (inferior) vestibular nucleus and the superior vestibular nucleus while the utricular nerve projects toward the medial, the superior vestibular nucleus, and rostral portion of the spinal vestibular nucleus (Fig. 1). These arrangements are consistent with the saccular projection that plays a role in the VCR mediated by the saccular macule, inferior vestibular nerve, the medial VST from the medial, inferior, and lateral vestibular nuclei, and finally the motor neurons of the accessory spinal nuclei

reaching the neck muscles. In contrast, the utricle contributes to the VOR that is transmitted through the MLF and other tracts in the dorsomedial brainstem. In monkeys, the principal cerebellar projection from the saccule is to the uvula with a less dense projection to the nodulus. In contrast, a strong projection from the utricle to the cerebellum is to the nodulus and weak projections are to the flocculus, paraflocculus, and uvula [12].

Selective stimulation of the utricular nerve in cats evokes excitatory postsynaptic potentials (EPSPs) at the ipsilateral lateral rectus motoneurons and small ocular counter-rotations [14, 15]. Utricular nerve stimulation also induces excitatory and inhibitory responses in the contralateral superior oblique motoneurons and the ipsilateral inferior oblique motoneurons which play a role in eye rotation during head tilt [15]. In cats, utricular stimulation evokes longer latency inhibitory postsynaptic potentials (IPSPs) in the contralateral extensor and flexor motoneurons [16] and in the SCM motoneurons, predominantly on the ipsilateral side [17]. In contrast, stimulation of the saccular nerve in cats induces no or only slight responses from the extraocular motoneurons in spite of the existence of a vertical VOR [18, 19]. Instead, the inhibitory disynaptic connections between the saccule and ipsilateral SCM motoneurons are strong enough to explain the underlying neural mechanism of cVEMPs in cats [20]. Therefore, these two sensory organs have rather different neural projections. There are strong projections of the utricular afferents to the oculomotor system and of the saccular projections to the cervical spinal neurons (Fig. 1).

Brainstem representation

cVEMPs

The topology of ischemic lesions for impaired cVEMPs was revealed in 29 patients with brainstem infarcts (Table 1) [11]. Using probabilistic lesion maps for unilaterally abnormal (12/29, 41.4 %) and normal cVEMPs (10/29, 34.5 %), the study showed that the lesions causing abnormal cVEMPs were mostly located in the areas of the vestibular nuclei and spinal accessory nerve in the lateral medulla oblongata. In the pons, the lesions were also frequently found in the anterolateral parts of the pyramidal tract fibers, and in the tegmental area of the pons, including the vestibular nuclei in a few patients. It is not surprising that lesions involving the vestibular nuclei at the level of the lateral lower pons or the spinal accessory nerve in the lateral medulla oblongata can impair cVEMPs (Fig. 2). However, more rostral brainstem lesions up to the mesencephalon may also impair cVEMPs [13, 21]. This suggests descending modulatory pathways for cVEMPs in the brainstem.

In another study, cVEMPs were abnormal in all lower brainstem lesions with decreased or absent wave formations or increased latencies [22]. In contrast, in patients with upper brainstem infarction, cVEMPs were normal while auditory brainstem reflexes were abnormal. The authors concluded that testing of cVEMPs is useful for identifying lower brainstem lesions.

oVEMPs

More than a half (27/52, 52 %) of the patients with acute brainstem lesions showed abnormal oVEMPs induced by air-conducted tone burst sounds (ACS) (Table 1) [5]. Four of the five patients with acute midbrain lesions (80 %) also showed abnormal oVEMPs during contralesional ear stimulation, mostly in combination with a contraversive ocular tilt reaction (OTR) and contraversive tilt of the subjective visual vertical (Fig. 2). Of the 28 patients with acute pontine lesions, 16 (57.1 %) showed abnormal oVEMPs. Responses were also abnormal in 47 % of the patients with medullary strokes. The majority of patients with abnormal oVEMPs to ACS had lesions in the dorsomedial brainstem that contains the MLF, the crossed ventral tegmental tract, and the interstitial nucleus of Cajal.

Lateral medullary infarction (Wallenberg syndrome)

Due to damage of the vestibular fascicles and vestibular nuclei that are involved in relaying and central processing of the peripheral vestibular inputs, lateral medullary lesions may cause abnormal VEMPs. One study showed that cVEMPs were abnormal in 43 % (9/21) of patients with lateral medullary infarction (LMI) (Table 1) [23]. The cVEMP abnormalities included decreased amplitude or delayed responses in the ipsilesional ($n = 5$), contralesional ($n = 2$), or on both sides ($n = 2$) (Fig. 2) [23]. However, only one patient (4.7 %) exhibited a canal paresis. In contrast to the cVEMPs, caloric tests evaluate the ascending horizontal VOR originating from the horizontal semicircular canal [20]. Therefore, in LMI, topographical correlations could be made that caloric paresis is more likely linked to rostrally located infarctions while absent or delayed cVEMPs may indicate caudally located ones [24]. The contralesional or bilateral abnormalities of cVEMPs in patients with unilateral LMI were ascribed to disruption of commissural modulation between the vestibular nuclei [23]. Of the 19 patients with medullary lesions, patients with lateral medullary lesions ($n = 14$) showed abnormal oVEMPs less frequently than those with medial medullary lesions (4/14, 28.5 % vs. 5/5, 100 %) [5].

Recently, two patients with isolated vestibular nuclear infarction showed decreased or absent responses of both

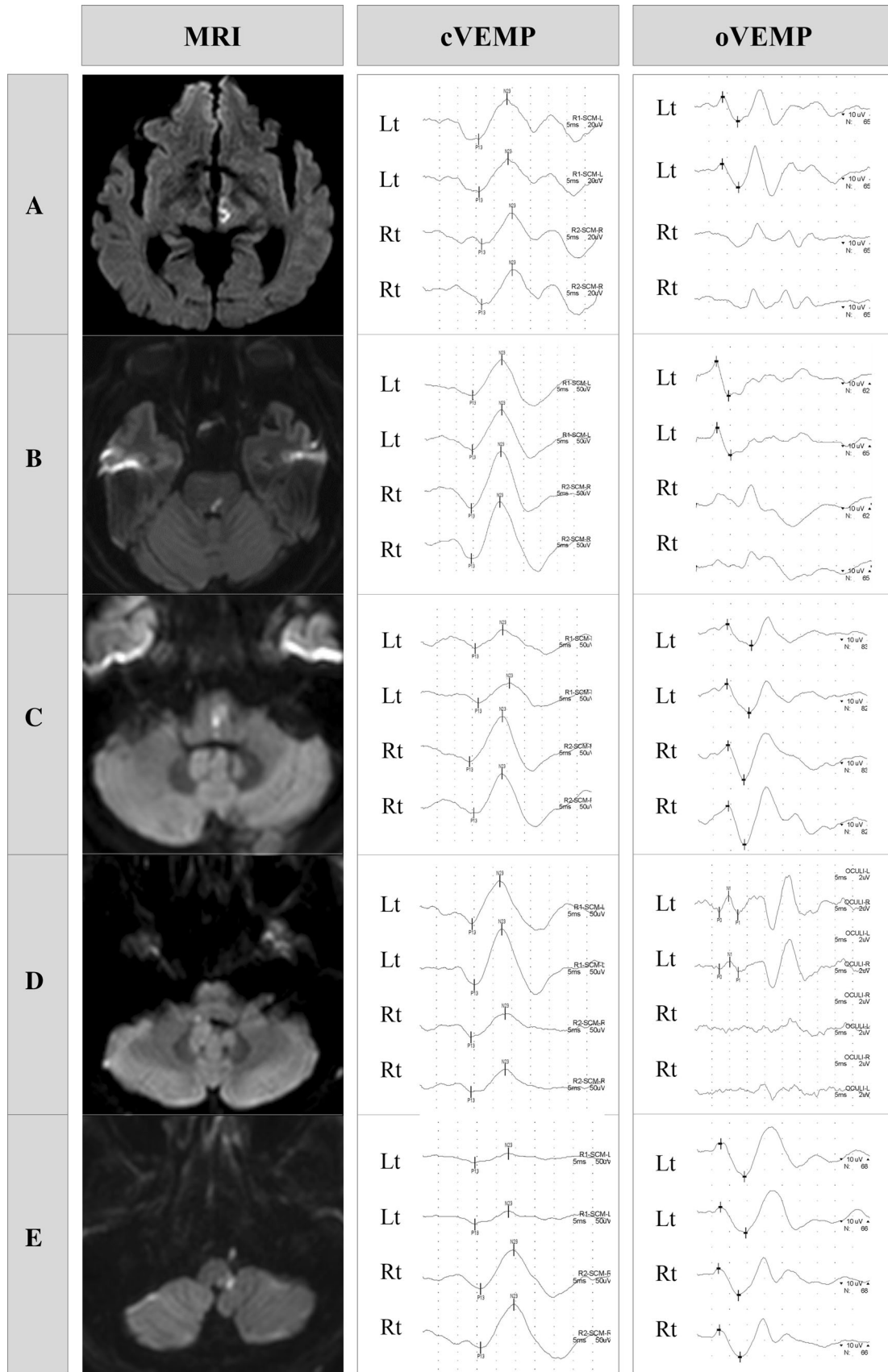


Fig. 2 Cervical and ocular vestibular-evoked myogenic potentials (VEMPs) from representative cases of brainstem infarctions at different anatomical locations. **a** A patient with acute midbrain infarction does not generate ocular VEMPs during contralesional ear stimulation, in combination with a contraversive ocular tilt reaction and tilt of the subjective visual vertical. **b** A patient with isolated unilateral internuclear ophthalmoplegia (INO) shows abnormal ocular VEMPs induced by air-conducted tone bursts during stimulation of the contralesional ear but sparing of cervical VEMPs. **c** A patient with medial medullary infarction (MMI) shows abnormal cervical VEMPs in the lesion side probably due to disruption of the medial vestibulospinal tract (VST) descending within the medial longitudinal fasciculus (MLF). **d** A patient with isolated vestibular nuclear infarction in the right side shows decreased cervical VEMPs and absent response of ocular VEMPs during tone burst stimulation of the ipsilesional ear (*right* ear). **e** A patient with acute infarction involving the lateral medulla shows decreased amplitude of cervical VEMPs during stimulation of the ipsilesional ear while the oVEMPs were symmetric. The side of VEMPs is indicated according to the ear stimulated

cervical and ocular VEMPs during tone burst stimulation of the ipsilesional ear [10]. They also exhibited spontaneous torsional-horizontal nystagmus that beat away from the lesion side, gaze-evoked nystagmus, ipsilesional canal paresis, and decreased head-impulse VOR gains for the horizontal and posterior semicircular canals on both sides, but more for the ipsilesional ones [10]. Thus, the lesions involving the vestibular nuclei may present features of both peripheral and central vestibulopathies including abnormal cVEMPs and oVEMPs during ipsilesional ear stimulation (Fig. 2).

Medial medullary infarction (MMI)

In about a half of the patients with MMI showed abnormal cVEMPs in the lesion side, and has been explained by disruption of the medial VST descending within the MLF (Fig. 2) [25]. The abnormal cVEMPs in patients with infarctions involving the medullary tegmentum support that cVEMPs are mediated by the medial VST descending within the MLF. Patients with abnormal cVEMPs frequently showed abnormal ocular motor findings, indicating that the lesions involved the medullary tegmentum in those patients.

Of the 19 patients with medullary lesions, all five with upper medial medullary lesions showed abnormal oVEMPs in response to ACS [5]. Three of them exhibited absent oVEMP formation only during contralesional ear stimulation while the other two had absent formation during stimulation of the ear on the lesion side or the ear on either side. These findings indicate a possible decussation of the otolithic fibers for oVEMPs in the upper medulla.

Internuclear ophthalmoplegia (INO)

One study evaluated 13 patients with internuclear ophthalmoplegia (INO) due to multiple sclerosis (MS) to determine whether oVEMPs are mediated by the MLF (Table 1) [26]. The study found that oVEMPs induced by ACS were more frequently abnormal (69 %) than cVEMPs (8 %). The oVEMPs in these patients were usually absent (13/26 ears) or delayed (5/26 ears) in 18 of the 26 ears (69.2 %). Another study found abnormal oVEMPs induced by ACS in 8 (67 %) of the 12 patients with isolated unilateral INO due to brainstem infarction [21]. In contrast, cVEMPs were abnormal in only 3 patients (25 %) (Fig. 2). The occasional abnormality of cVEMPs in these patients suggests a modulatory pathway for the inhibitory sacculocollic reflex descending in the MLF [21]. A recent study also showed absent oVEMPs in response to ACS during contralesional ear stimulation in all 7 patients with unilateral INO and no wave formation on both sides in another patient with bilateral INO [5]. Two patients with one-and-a-half syndrome exhibited absent or delayed responses of oVEMPs only during contralesional ear stimulation. All these findings support that oVEMPs are mediated by the fibers ascending in the MLF.

Cerebellar representation

The cerebellum has reciprocal connections with the vestibular nuclei and plays a major role in balance control [27]. The saccular nerve has a strong projection to the uvula and nodulus, and the utricular nerve to the nodulus, uvula, flocculus/paraflocculus, and bilateral fastigial nuclei [12, 28]. In monkeys, the cerebellar vermis and flocculus have direct and indirect projections to the vestibular nuclei [29]. In general, the flocculus is important for control of the angular VOR, while the nodulus and uvula are mainly involved in the control of otolith-related reflexes [30]. Therefore, in addition to conventional neurotologic tests, evaluation of VEMPs can provide valuable information for understanding the pathomechanism of cerebellar disorders.

cVEMPs

Cerebellar lesions in the non-AICA (anterior inferior cerebellar artery) territories have generally been known to spare cVEMP responses (Table 1) [31, 32]. In a previous study, the mean p13 latencies and peak-to-peak amplitudes did not differ between the patients with cerebellar stroke and controls [32]. There were no differences in the latency or amplitude between the ipsi- and contralesional sides

Table 1 Findings of cVEMPs and oVEMPs in brainstem and cerebellar lesions

References	Pathology	Stimulus	Abnormal cVEMPs	Abnormal oVEMPs	Comments
Brainstem lesions					
Heide et al. [11]	Infarction	Clicks	19/29 (65.5 %, unilateral in 12, bilateral in 7)	n/a	cVEMPs may be affected by lesions above the level of the vestibular nuclei
Oh et al. [5]	Infarction	Tone burst (500 Hz)	n/a	28/52 (53.8 %)	The majority of patients with abnormal oVEMPs had lesions in the dorsomedial brainstem.
Kim et al. [23]	LMI	Tone bursts (500 Hz)	9/21 (43 %, unilateral in 7, bilateral in 2)	n/a	cVEMP was abnormal on either side.
Tseng et al. [24]	LMI	Tone bursts (500 Hz)	3/5 (60 %, absent or delayed)	n/a	Caloric areflexia in rostral infarction, abnormal cVEMPs in caudal infarction
Kim et al. [25]	MMI	Tone bursts (500 Hz)	7/14 (50 %)	n/a	Abnormal cVEMPs in lesions involving the tegmentum, probably due to damage to the MLF
Rosengren et al. [26]	MS with INO	Tone bursts (500 Hz)	2/26 sides (8 %)	18/26 sides (69 %, absent in 13, delayed in 5)	Abnormal unilateral oVEMPs in patients with INO due to multiple sclerosis
Kim et al. [21]	Infarction with isolated INO	Tone burst (500 Hz)	3/12 (25 %)	8/12 (67 %)	oVEMPs appear to be mediated by the crossed VOR pathways running in the MLF
Cerebellar lesions					
Pollak et al. [32]	Infarction	Clicks	None	n/a	Normal cVEMPs in cerebellar strokes
Ahn et al. [33]	AICA infarctions (brainstem spared)	Clicks	8/16 (50 %, ipsilesional), no difference in latency	n/a	Abnormal cVEMPs more frequently observed in patients with CP than those without
Su et al. [39]	cerebellar lesion	BCV	75 % of patients with extension into the brainstem, none with localized cerebellar lesion	88 % with extension into the brainstem, none with localized cerebellar lesion	Abnormal VEMPs only when the lesions involved the brainstem
Kirchner et al. [35]	Cerebellar ataxia, bilaterally pathological HITs	Clicks	22/31(71 %)	n/a	Impaired cVEMPs on both sides in all with complete bilateral vestibulopathy
Choi et al. [34]	Acute unilateral cerebellar infarctions	Tone bursts, Tapping the Fz	11/27 (41 %)	9/27 (33 %)	More frequent abnormalities of VEMPs in patients with the OTR/SVV tilt than those without

AC air-conducted, BCV bone-conducted vibration, VEMP vestibular-evoked myogenic potentials, MLF medial longitudinal fasciculus, CVTT the crossed ventral tegmental tract, LMI lateral medullary infarction, MMI medial medullary infarction, INO internuclear ophthalmoplegia, AICA anterior inferior cerebellar artery, CP caloric paresis, BCV bone-conducted vibration, HIT head-impulse test, OTR ocular tilt reaction, SVV subjective visual vertical, n/a not assessed

either. However, in AICA territory infarctions, the abnormal cVEMP responses can be explained by concomitant inner ear involvements [33]. The cVEMPs induced by click sounds were recorded in 16 patients with unilateral AICA territory infarction, and 50 % of them exhibited abnormal responses including absent or decreased amplitude on the side of infarction [33]. Patients with abnormal cVEMPs more frequently had canal paresis or sensorineural hearing loss compare to those with normal cVEMPs. This suggests that abnormal cVEMPs might result from ischemia to the peripheral vestibular system from the root entry zone of the eight nerves to the inner ear [33]. Twenty-seven patients with acute unilateral cerebellar infarctions were subjected to cVEMPs in response to ACS and oVEMPs induced by bone-conducted vibration [34]. In this study, the patients with the OTR showed abnormal VEMPs more frequently than those without (11/15 vs. 3/12, respectively). This study also revealed frequent abnormalities of cervical (11/27, 41 %) and ocular (9/27, 33 %) VEMPs in patients with unilateral cerebellar infarction. However, the absence of correlation in the directionality between the OTR and VEMP abnormalities suggests either deactivation or disinhibition as the cerebellar role in otolith modulation [34].

In patients with cerebellar ataxia and bilaterally impaired head-impulse tests, cVEMPs were abnormal in 71 % (22/31), reduced amplitude in 18 and absent responses in 7, either bilaterally ($n = 13$) or unilaterally ($n = 9$) [35]. In this report, voxel-based morphometry revealed a cerebellar atrophy in both the vermis and cerebellar hemispheres, especially in the flocculi on both sides, which could have contributed to abnormal vestibulo-collic responses [35]. Studies of the patients with spinocerebellar degeneration including olivo-ponto-cerebellar atrophy (OPCA, $n = 10$), cortical cerebellar atrophy (CCA, $n = 3$), and Machado–Joseph disease (MJD, $n = 3$) showed that patients with OPCA and CCA had well-preserved cVEMPs while two of the three patients with MJD had abnormal results [36]. Some cerebellar patients may show dissociation between canal and otolith dysfunction [37].

oVEMPs

It remains unclear whether the cerebellum has any influence on the oVEMP responses. However, damage to the cerebellum has been implicated as a cause of skew deviation and OTR which have been attributed to asymmetric modulation of the vestibular projections from the receptors of the utricle [38]. The primary utricular afferents have strong direct projections to the vestibular nuclei, the cerebellar nodulus, and ventral uvula and weaker projections to the anterior vermis, the fastigial nuclei, and the flocculus

and ventral paraflocculus [12]. Lesions of the nodulus or uvula may affect the otolith-ocular reflexes and oVEMPs [30]. A study found absent oVEMPs in patients with cerebellar lesions extending into the brainstem, but normal responses in patients with isolated cerebellar lesions [39]. Abnormal VEMPs in isolated cerebellar lesions suggest a ‘modulatory role’ of the cerebellum on the otolith function, or some cases of technically abnormal VEMPs, or perhaps the lesions larger than they appear on imaging.

Multiple sclerosis

Patients with MS frequently report dizziness and disequilibrium related to vestibular dysfunction in the course of their illness [40]. Although they do not always show brainstem or cerebellar lesions on imaging studies, the vertigo and imbalance mostly arise from structural or functional involvement of the vestibular system. Patients with lesions involving the VOR and vestibulospinal reflex (VSR) pathways may show various degrees of functional impairment. Therefore, investigations of cervical and ocular VEMPs are useful in assessing the VOR and VSR pathways in MS patients.

cVEMPs

Three patients with definite MS and MRI lesions involving the VST showed a prolonged latency of cVEMPs (Table 2) [41]. This could be attributed to demyelination of either the primary afferent axons at the root entry zone or the secondary VST axons rather than to the lesions involving the vestibular nucleus neurons. Another study of 40 MS patients found abnormal cVEMPs in 28 patients (70 %) [42]. In 24 (85.7 %) of them, the cVEMPs were delayed on one or both sides, and were not generated at all on one side in the remaining 4 patients. These results were concordant with the clinical findings of brainstem involvement in 55 % and with the abnormal MRI findings in 65 % of the cases [42]. In contrast to most previous studies with MS patients that showed increased latencies of cVEMPs, one retrospective study involving 70 MS patients described abnormal cVEMPs in 31 % of them, but increased latencies only in 11.8 %, and reduced peak-to-peak amplitude or absent responses in 19.1 % [43]. The absent cVEMPs might have been caused by axonal damage or severe loss of the myelin sheaths.

A previous study attempted to determine whether VEMPs are useful in detecting “silent” demyelinating lesions involving the brainstem in MS patients [44]. The study found that only those with a history or symptoms/signs of brainstem dysfunction showed abnormal cVEMPs while those without did not show differences in the VEMP

Table 2 Comparative data for cVEMPs and oVEMPs in patients with multiple sclerosis and vestibular migraine

References	Stimulus	Abnormal cVEMP	Abnormal oVEMP	Comments
Multiple sclerosis (MS)				
Shimizu et al. [41]	Clicks	3/3, (100 %, prolonged latencies)	n/a	
Alpini et al. [42]	Clicks	28/40 (70 %, prolonged latency in 24, absent responses in 4)	n/a	
Versino et al. [43]	Clicks	22/70 (31.4 %, prolonged latencies in only 11.8 %)	n/a	
Gabelic et al. [47]	Clicks	Prolonged latencies in 57 %, absent responses in 7 %	Prolonged latencies in 30 %, absent responses in 40 %	When cVEMPs and oVEMPs were combined, 80 % showed abnormal findings
Gazioglu et al. [48]	Clicks	11/62 (18 %)	28/62 (45 %)	Both ocular and cervical VEMP latencies were significantly correlated with EDSS
Bandini et al. [44]	Clicks	16/36 (43 %, delayed latency)	n/a	Only those with brainstem involvements showed abnormally increased p13 latency
Vestibular migraine (VM)				
Baier et al. [51]	Tone bursts (400 Hz)	43/63 (68 %, reduced amplitudes), No latency difference	n/a	VM patients revealed significantly and bilaterally reduced cVEMP amplitudes
Baier and Dieterich [52]	Tone bursts (400 Hz)	43/63 (68 %) in VM, 11/16 (69 %) in MD, reduced amplitude	n/a	Sacculi may be affected in both VM and MD
Zuniga et al. [54]	Clicks and Tone bursts(500 Hz)	Reduced amplitudes ($p < 0.001$)	Reduced click-evoked, normal in tone-evoked & vibration-evoked amplitudes.	VM and MD behaved similarly on most of the VEMP tests
Taylor et al. [55]	Clicks and BCV	No differences	No differences	
Bolding et al. [53]	Clicks	16/37 (44 %, absence response) in VM, 8/32 (25 %) in migraineurs, 3 % in healthy controls	n/a	

MS multiple sclerosis, EDSS expanded disability status scale, VM vestibular migraine, BCV bone-conducted vibration

findings compared to normal controls [44]. The abnormalities were mostly delayed responses ($p < 0.001$) rather than reduced amplitudes. Overall, a number of studies showed abnormal cVEMPs in 31–70 % of patients with definite MS [42–46]. Delayed responses were the most frequent abnormality but showed little correlation with the radiological findings in most studies [42–46].

oVEMPs

Regarding oVEMPs, prolonged latency was found in 30 % and absent response in 40 % of patients on at least one side in a study of 30 MS patients [47]. The mean latencies of oVEMPs and cVEMPs were significantly increased in MS patients, and also correlated with the expanded disability status scale (EDSS) [47]. Another study of 62 MS patients found a higher prevalence of abnormal oVEMPs than abnormal cVEMPs (45.2 vs. 17.7 %, $p < 0.01$) [48]. In this study, the abnormalities were mostly increased latencies rather than reduced amplitudes. Although correlations with clinical or MRI evidence of brainstem involvements were not significant, both ocular ($p < 0.05$) and cervical VEMP latencies ($p < 0.01$) were significantly correlated with EDSS. These results appear to indicate the possibility of asymptomatic or pre-radiological involvement of the vestibulocollic or VOR pathways in MS patients. Another study found a higher frequency of abnormalities in oVEMP (69 %) than in cVEMPs (8 %) in patients with INO mostly due to MS [26]. These findings may be ascribed to the lesions mostly located in the upper brainstem.

Increased latency of VEMPs, however, is not specific for MS, and does not help distinguishing MS from other etiologies because prolongation of the latency has been reported in other pathologies affecting the brainstem, such as strokes and tumors [49].

Vestibular migraine

Patients with acute vestibular migraine (VM) may show clinical signs suggestive of central as well as peripheral vestibular dysfunction [50].

cVEMPs

One study showed that cVEMP amplitudes were reduced in 43 (68 %) of the 63 patients with VM while the latencies were within normal range (Table 2) [51]. In this study, the reduced cVEMP amplitudes in the presence of normal latencies suggest hypoperfusion-induced ischemia or serotonergic-induced extravasation of the inner ear affecting the saccule. They also compared the findings of cVEMPs induced by ACS between the patients with VM

and Meniere disease (MD) to determine electrophysiological differences between the two disorders (Table 2) [52]. Similar prevalence of reduced cVEMP amplitude was found between the patients with VM (68 %, 43/63) and MD (69 %, 11/16), but the latencies were within normal range [52]. These results suggest that the saccule or its afferent pathway may be affected in both disorders, and probably due to labyrinthine pathogenesis.

Compared to ordinary migraineurs and healthy controls, VM patients frequently show absence of cVEMP responses (16/37, 44 % in VM, vs. 8/32, 25 % in the migraineurs vs. 3/30, 3.3 % in the controls) even though the sound intensity thresholds and latencies of cVEMPs were similar among the groups [53] (Table 2).

oVEMPs

Even though both VM and MD groups showed significantly reduced cVEMP and oVEMP amplitudes in recent studies [52, 54], there were some differences in the result of VEMPs in response to different stimulus modalities [54, 55]. During stimulation with click-evoked sounds, the amplitudes of both cVEMPs and oVEMPs were significantly reduced in both VM and MD groups compared with controls [54]. In contrast, the VM group did not show a difference in oVEMPs induced by tone burst sounds while patients with MD showed a significant reduction in oVEMP amplitudes. However, when stimulated with bone-conducted vibration (BCV) using a tendon hammer or a Mini-Shaker at the midline forehead, the amplitude of oVEMPs did not show any differences between the VM and MD groups [54]. Another study did not show any difference in the amplitudes or symmetry of oVEMPs among the controls, VM and MD either [55]. These results suggest that, compared to MD, VM may show fewer abnormalities of both cVEMPs and oVEMPs in response to click sounds and cVEMPs induced by minitaps. Therefore, although VM and MD behave similarly on most of the VEMP tests, further studies adopting different stimuli are required to resolve this issue in larger number of patients.

Cortical representation

The significant overlap of utricular and saccular afferents in the vestibular nuclei suggests a convergence of these inputs for functional integration of the vestibular reflexes [12]. The cortical representation of the semicircular canals or the entire vestibular nerve has been demonstrated using caloric activation and galvanic stimulation [56, 57].

The ascending cortical projections of the otoliths were demonstrated with cVEMPs induced by ACS using fMRI [58, 59]. These studies found a significant activation in the

multisensory cortical vestibular network within both hemispheres, including the posterior insular cortex, the middle and superior temporal gyri, and the inferior parietal cortex [58]. The activation was bilateral with a predilection for the right hemisphere in right-handers and with a predominant ipsilateral projection. These patterns of cortical activation are very similar to those with galvanic and caloric stimulations [56, 57, 60]. This indicates that the semicircular canal and otolith inputs may converge at the brainstem level, e.g., within the vestibular nuclei, and reach the vestibular cortical areas as integrated information.

However, we should interpret the VEMP results with caution since: (1) Much of the data are from studies using ACS to stimulate the vestibular receptors. Several control studies on healthy individuals have shown the high false positive abnormal rate of VEMPs in response to ACS, whereas they do have clear responses to BCV [61]. (2) Most studies do not have an age-matched control group, and the VEMP amplitudes were not normalized. (3) Most studies involved measuring VEMPs in a small group of non-randomly selected patients with a specific diagnosis (e.g., MS) or lesion site (e.g., brainstem), which make it impossible to extrapolate the sensitivity and specificity of particular VEMP abnormalities for a specific diagnosis. (4) Definitions of the abnormalities regarding the latency and amplitude are not clear. (5) Lack of standardization of VEMP techniques and analysis makes it difficult to compare the findings among the studies. To improve consistency of the recordings within and among the laboratories, standardized minimum requirements and guidelines are required for proper recording and interpretation of VEMPs [62].

In conclusion, cervical and ocular VEMPs appear to be effective in evaluating the function of central vestibular pathways, especially in the patients with brainstem or cerebellar lesions. Cervical VEMPs provide a valuable tool for investigating the integrity of the vestibulo (sacculo)-spinal pathways [11], while oVEMPs reflect the function of the vestibulo (utrículo)-ocular pathways (Fig. 1) [5]. Combined evaluation of ocular and cervical VEMPs permits assessment of both ascending and descending vestibular pathways in the brainstem and should be considered an important neurophysiological tool for investigating the central vestibulopathies. These evoked potentials may be even useful in detecting central vestibulopathies that are not readily defined by conventional vestibular function tests. However, we still await well-designed studies with standardization of the measurements and analyses, and with age-matched normal controls.

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Compliance with ethical standards

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