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RESEARCH ARTICLE

Utricular function in vestibular neuritis: a pilot study of concordance/discordance between ocular vestibular evoked myogenic potentials and ocular cycloposition

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Abstract
Vestibular neuritis (VN) can affect utricular afferents. Utricular function can be assessed by ocular vestibular evoked myogenic potentials (oVEMPs) whose abnormalities include weak or absent responses, and ocular cycloposition whose abnormalities include ocular torsion (OT). When studied independently in vestibular neuritis, oVEMPs are abnormal in 61–82% of cases, and OT is present in 72–80% of cases. The similar range of abnormalities suggests the hypothesis that these tests should be concordantly abnormal. We tested this hypothesis by identifying consecutive adult cases of VN in whom both oVEMPs and OT were performed. OT and oVEMP overlapped (both were abnormal) in only 47% of cases. In 40% of cases oVEMPs alone were abnormal, and in 13% of cases, OT alone was present. These results suggest that oVEMPs and OT assess different aspects of utricular function believed to arise from discrete zones of the utricular macula; the former are thought to reflect the activity of extra-striolar afferents (which detect constant acceleration), and the latter reflects the activity of striolar afferents (which detect change in acceleration).

Keywords Utricle · Vestibular neuritis · Vestibular function · Evoked potential · Ocular torsion

Introduction

The utricle detects linear acceleration along the lateral and anterior–posterior axes. Existing objective tests of its function that are practical for clinical use include ocular vestibular evoked myogenic potentials (oVEMP) and measurement of ocular cycloposition. Other methods applicable to testing utricular function are either of very limited availability—such as the unilateral centrifugation protocol in off-axis rotatory chair testing (Clarke et al. 2003)—or are mostly restricted to research settings—such as sleds (von Baumgarten and Thumler 1979), human centrifuges (Brandt 1962) and Moog platforms (Mardirossian et al. 2014). Lesions of the vestibular system can involve the end-organ (labyrinth), the afferent pathways (vestibular nerve) or central structures (vestibular nuclei in the brainstem). When a lesion involves one or more elements along these utricular pathways, at least initially the clinical tests of utricular function may be abnormal; specifically, oVEMPs may be reduced or absent, and tests of ocular cycloposition may show static ocular cyclodeviation, also termed ocular torsion (OT). Since utricular afferents comprise 32% (Bergström 1973)–34% (Lee et al. 1990) of the entire vestibular nerve, one would expect tests of utricular function to be sensitive to lesions of the vestibular nerve, as occurs in vestibular neuritis.

The technique for performing oVEMP is fairly well standardized and is becoming increasingly available in clinical vestibular laboratories (Curthoys 2017; Fife et al. 2017).

Examination of OT (i.e., abnormal ocular cycloposition) is not regularly performed in most clinical vestibular laboratories. There are several methods for detecting OT. An easy but subjective method involves having the patient "dial" an indicator of what he or she perceives to be vertical or horizontal—these tests are the subjective visual vertical (SVV) (Bohmer 1999; Vibert et al. 1999; Ogawa et al. 2012) and subjective visual horizontal (SVH) (Tribukait et al. 1998; Takai et al. 2006); however, these subjective

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tests do not always match true vertical or horizontal (Poljac et al. 2005; Kheradmand and Winnick 2017; Kim and Kim 2018) due in part to additional perceptual processing. An objective way of measuring ocular cycloposition is to image the retina and calculate the disc–foveal angle—the angle formed by the intersection of one line drawn through the center of the optic disc and the center of the fovea, and a second line representing earth horizontal. The most common imaging modality for this purpose is visible light retinal photography, though optical coherence tomography (OCT) can be used for this as well. Note that we are studying ocular torsion rather than the more complex phenomenon of the ocular tilt reaction (OTR); the latter is more common in posterior fossa lesions, and is reported relatively rarely in cases of unilateral vestibular deafferentation (Halmagyi et al. 1979, 1991; Vibert et al. 1996; Goto et al. 2011).

Studies of ocular vestibular evoked myogenic potentials in vestibular neuritis report weakness or absence of a response on the affected side in 61–82% of cases (Choi et al. 2007, 2015; Kim et al. 2008). Studies of ocular cycloposition in vestibular neuritis report ocular torsion towards the affected side in 72–80% of cases (Magliulo et al. 2014; Taylor et al. 2016). These ranges are fairly similar, so one might reasonably hypothesize that in cases of vestibular neuritis, abnormalities in these two tests of utricular function should be concordant—in other words, if one is abnormal, then the other should also be abnormal.

Surprisingly, there are very few data in the literature about whether such concordance holds. There have been studies of oVEMP and OT in cerebellar infarctions (Choi et al. 2014); there have been studies of cervical VEMP (cVEMP) and OT in vestibular neuritis (Kim et al. 2008); there have been studies of SVV and OT in vestibular neuritis (Choi et al. 2007); there is a case report of oVEMP and OT in labyrinthitis (Goto et al. 2011); but to our knowledge there have been no systematic studies directly comparing these two tests of utricular function (oVEMP and OT) in vestibular neuritis, so we decided to explore how often they are concordantly abnormal (i.e., ocular vestibular evoked myogenic potentials are absent or weak, and there is also ipsiversive ocular torsion).

Hypothesis

Our hypothesis was that in cases of unilateral vestibular neuritis, if utricular afferents are involved, then tests of utricular function (oVEMP and ocular cycloposition) should both be abnormal (i.e., ocular vestibular evoked myogenic potentials should be weak or absent, and OCT should show ipsiversive OT).

Setting, materials and methods

We conducted a study of consecutive adult patients (age 18 years or older) evaluated in our university-affiliated otoneurology clinic who presented following an acute vestibular syndrome (Hotson and Baloh 1998; Kattah et al. 2009), who had no auditory symptoms; who had undergone a standard otoneurological clinical examination, in whom measurements of oVEMP and ocular cycloposition by OCT were obtained, in whom at least one of these tests was abnormal, who were diagnosed with vestibular neuritis, and in whom there was no evidence to support an alternative diagnosis. We were not seeking to determine the overall sensitivity of oVEMP and ocular cycloposition for vestibular neuritis (which has been described elsewhere), but rather were trying to assess how frequently they were concordantly abnormal. Consequently, we excluded patients in whom both tests were normal (i.e., in which presumably there was no evidence of involvement of utricular pathways). We also excluded patients with diagnosed or suspected neurological disease (e.g., infarction, demyelination, space-occupying lesions or neurodegenerative disorders), diagnosed or suspected otologic disease besides vestibular neuritis (e.g., conductive hearing loss, Ménière's disease, superior semicircular canal dehiscence, vestibular schwannoma), and diagnosed or suspected ocular disease (e.g., strabismus, myasthenia gravis, blindness, or retinal disease that could make it infeasible to determine the disc–foveal angle). We identified 15 patients (10 female), age range 25–75 years (median 56 years) who met all of the inclusion criteria and had none of the exclusion criteria. The study was granted an exemption by our university's institutional review board on the basis of it being a case series (IRB STU00207680).

We acquired oVEMPs using the Navpro system of Bio-Logic (Mundelein, Illinois). Our laboratory's upper normal limit of amplitude asymmetry was 35%.

Retinal imaging was acquired using the optical coherence tomography system by Heidelberg Spectralis (Heidelberg, Germany), whose software platform automatically calculates the disc–foveal angle. We used Brandt and Dieterich's normative ranges for ocular cycloposition (Brandt and Dieterich 1993) in which the right eye's position is $4.9° \pm 2.9°$ (95% CI $-1.0°$ to $+11.0°$), and the left eye's position is $5.7° \pm 2.9°$ (95% CI $0.0°$ to $+11.5°$). By convention, a positive disc–foveal angle signifies excyclotropia (the macula is lower than the optic disc), while a negative disc–foveal angle signifies incyclotropia (the macula is higher than the optic disc). We classified as abnormal any patient in whom one or both eyes exhibited a disc–foveal angle outside of the 95% confidence interval.

Results

The results are shown in Table 1. It is known that both oVEMPs (Magliulo et al. 2014) and OT (Choi et al. 2007; Kim et al. 2008) can improve over time; consequently, we list how long after symptom onset each test was performed. It would be desirable for these tests to be performed simultaneously and at a specific interval after symptom onset, but we do not have control over such timing since we can only evaluate patients as they are referred to us, and since we need in turn to refer patients to the ophthalmology clinic to undergo OCT. A comparison specifically between oVEMP and ocular cycloposition (assessed by OCT) is shown in Table 2, with ancillary information from other vestibular tests where available.

Discussion

In our data of patients with unilateral vestibular neuritis exhibiting oVEMP weakness/absence, or ocular torsion or both, oVEMPs were abnormal in 87% of cases and OT was present in 60% of cases. Note that this differs from the previously mentioned figures from other studies whose goals instead were to describe the percentage of all vestibular neuritis cases in which one or the other test was abnormal [ocular vestibular evoked myogenic potentials were weak or absent in 61% (Choi et al. 2015), 72% (Choi et al. 2007) and 82% (Kim et al. 2008) of cases; ocular torsion was present in 72% (Taylor et al. 2016) and 80% (Magliulo et al. 2014) of cases].

Our data show that oVEMP and OCT overlapped (both were abnormal) in only 47% of cases. In 40% of cases, oVEMPs alone were abnormal, and in 13% of cases, OCT alone was abnormal (OT was present). In other words, oVEMP and OT are both abnormal in just under half of cases, but each test can be abnormal independently of the other. Our original hypothesis that the tests would be concordantly abnormal was incorrect. We considered several different conjectures to account for this difference.

The incomplete overlap between results of oVEMP and OCT may in part be due to the fact that these tests actually assess different aspects of utricular function. Careful studies across multiple species (Goldberg et al. 1990; Si et al. 2003; Huwe et al. 2015) show that the "units" (afferent neuron plus the hair cells it innervates) in the striolar zone and extra-striolar zones of the utricular macula have distinct architectural, mechanical and physiologic characteristics (Fernandez et al. 1972; Fernandez and Goldberg 1976a, b), such that the units in the extra-striolar zones detect constant acceleration, whereas those in the striolar zone detect "jerk" (change in acceleration) (Gresty et al. 1992; Curthoys 2017). Ocular cycloposition in the coronal plane partially reflects the function of extra-striolar afferents, whereas oVEMPs partially reflect the function of striolar afferents. The detection of constant acceleration is referred to as a "static"/"sustained" vestibular sensory function, whereas the detection of changing acceleration is referred to as a "dynamic"/"transient" vestibular sensory function (Curthoys and Halmagyi 1995; Curthoys et al. 2017). Grant and Curthoys (2017), and Curthoys et al. (2018) have advanced the idea that there is an even more fundamental physiologic difference between the end-organ receptor mechanics that generate the input whose response these tests measure, with the static/sustained function serving the role of an accelerometer (in which the otoconia are moved relative to the hair cells), and the dynamic/transient function serving the role of a seismometer (in which the hair cells move with respect to the otoliths whose inertia keeps them stationary).

Recognizing the different utricular functions reflected in the results of oVEMP and OCT may be part of the answer to the question of why their results can be discordant, but leads to a different problem, namely how can vestibular neuritis differentially affect these distinct utricular functions? There are several possible explanations to consider.

One possible explanation offered in the literature is that in recovery from vestibular neuritis, compensation for static/sustained vestibular function differs from that for dynamic/transient vestibular function (Choi et al. 2007), and that in some instances the compensation will succeed for one but fail in the other. That the neurologic mechanisms for static versus dynamic compensation differ has been generally accepted (Curthoys 2000). Regarding compensation of static/sustained vestibular function, Ward and colleagues (Ward et al. 2017), citing animal studies (Galiana et al. 1984; Fetter and Zee 1988), comment that "For static, set-point adaptation of the VOR (vestibulo-ocular reflex), there must exist a mechanism that monitors the spontaneous neural discharge occurring at the vestibular nuclei to rebalance the activity between the two sides. The commissural system between the vestibular nuclei may mediate the rebalancing of activity". Regarding compensation of dynamic/transient vestibular function, they add that for "adaptation of the gain of an inappropriate VOR, signals of unwanted retinal image motion during head movements are thought to be received by the cerebellum that, in turn recalibrates the eye movement response"; Leigh and Zee (2015) elaborate that this type of compensation requires the integrity of the nucleus of the optic tract (Yakushin et al. 2000; Stewart et al. 2005) and its projections to the cerebellum. One way of checking this would be to perform prospective studies of patients with vestibular neuritis in whom initially oVEMPs are weak or absent on one side, and ocular torsion towards the same side

Table 1 Series of patients diagnosed with unilateral vestibular neuritis

No.	Age	Gender	Optical coherence tomography			Ocular vestibular evoked myogenic potentials		Videonystagmography		Video head impulse testing			Cervical vestibular evoked myogenic potentials	
			DFA, R	DFA, L	Time after onset	Result	Time after onset	Caloric	Time after onset	Gain	Saccades	Time after onset	Result	Time after onset
1	71	M	12.2	1.4	1 month	R 58% weakness	1 month	R 94% weakness	1 month	R gain 0.26	R overt	1 month		
2	75	F	12.1	4	5 months	R absent	6 months	Normal	6 months	–	–			
3	42	F	− 4.43	13.3	1 month	L 61% weakness	1 month	L 72% weakness	1 month	L gain 0.44	L overt	1 month		
4	75	F	7	6.2	11 months	R 50% weakness	11 months	R 85% weakness	10 months	R gain 0.67	R overt	10 months	R 45% weakness	10 months
5	45	M	2.7	13.4	2 months	L absent	2 months	L 86% weakness	2 months	L gain 0.37	L overt	2 months		
6	56	F	0.3	9.3	9 months	L 42% weakness	9 months	Normal	9 months	Normal	L overt	9 months		
7	70	F	11.8	0.9	20 days	R absent	48 days	R 76% weakness	48 days	R gain 0.33	R overt	20 days		
8	42	M	13.9	7.1	7 days	Normal	6 days	R 28% weakness	6 days	Normal	R overt	6 days		
9	49	M	− 3.4	7.9	6.5 months	L absent	6.5 months	L 100% weakness	2.5 months	L gain 0.57	L overt	6.5 months	Normal (33% L weakness)	7 months
10	74	M	8.2	0.3	33 months	R absent	33 months	78% R weakness	4 months	R gain 0.52	R overt	33 months		
11	60	F	7.9	5.7	15 months	R absent	14 months	Not done	–	R gain 0.46	R covert and overt	14 months		
12	60	F	9.0	5.1	19 days	R 75% weakness	10 days	71% R weakness	10 days	R gain 0.33	R covert and overt	10 days		
13	52	F	14.2	7.6	3 months	R absent	86 days	–	–	R gain 0.46	R covert and overt	93 days	R absent	93 days
14	50	F	2.9	5.7	56 days	R 48% weakness	56 days	Normal	56 days	Normal	Normal	56 days	Normal	55 days
15	25	F	− 3.2	14.1	6 days	Normal	16 days	L 44% weakness	16 days	L gain 0.71	L covert	16 days	L absent	6 days

DFA disc–foveal angle

Table 2 Comparison of oVEMP and OCT

	oVEMP abnormal (absent or reduced)	oVEMP normal (present and symmetrical)	
OCT abnormal (ocular torsion present)	oVEMP and OCT both abnormal in 7/15 (47%)	OCT alone abnormal in 2/15 (13%)	OCT abnormal in 9/15 (60%)
OCT normal (ocular torsion absent)	oVEMP alone abnormal in 6/15 (40%)		
	oVEMP abnormal in 13/15 (87%)		

oVEMP ocular vestibular evoked myogenic potentials, *OCT* optical coherence tomography

is also present, and then follow these patients longitudinally to monitor what percentage of patients exhibit improvement in neither, or in just one, or in just the other. However, even if such studies verify consistently different rates of compensation, this still defers the question to one of why compensation for one type of function succeeds while the other fails. Moreover, the claim that static/sustained vestibular functions (such as that reflected in ocular torsion) recover more rapidly than dynamic/transient vestibular functions (such as that measured by oVEMP) (Choi et al. 2007), while often true, may not be an inviolable rule; our data provide some examples on the contrary. For instance, in patient 8, OCT was performed at day 7 after symptom onset and was abnormal while oVEMPs were performed at day 6 after symptom onset and were normal; similarly, in patient 15, OCT was performed at day 6 after symptom onset and was abnormal while oVEMPs were performed at day 16 after symptom onset and were normal. These data suggest that the idea that static/sustained vestibular function recovers more rapidly than dynamic/transient vestibular function captures a general tendency but may not be universally correct.

A second possible explanation pertains to the discreteness and consistency of the lesion in vestibular neuritis. If one assumes that vestibular neuritis consists of a discrete and consistent lesion, then one might conclude that all nerve fibers within that lesion should be affected and, indeed, of the few histopathological studies available from autopsy specimens, some show a fairly diffuse affectation of the vestibular nerve (Morgenstein and Seung 1971; Friedmann and House 1980; Baloh et al. 1996; Richard and Linthicum 2012). If the lesion is more restricted (i.e., does not involve the entire nerve), then conceivably it could affect an area where the striolar afferents and extra-striolar afferents are relatively segregated from each other. Another possibility, suggested by histopathological studies demonstrating more scattered or heterogeneous damage (Gacek 1999; Gacek and Gacek 2002), is that the lesion is actually inconsistent, perhaps exhibiting trophism for particular fiber types. Additional autopsy studies may help shed light on this question, but such data emerge rarely. High-resolution MRI cross sections through the internal auditory canal (Fundakowski et al. 2012) are still insufficient to characterize this level of detail. Studies using MRI with high-dose gadolinium, seeking enhancement of the vestibular nerve, report inconsistent results (Hasuike et al. 1995; Strupp et al. 1998; Karlberg et al. 2004), and in any case are still of insufficient resolution to answer this question. It is conceivable that diffusion tensor tractography MRI of the vestibular nerve (Yoshino et al. 2015) will eventually be more revealing in this regard.

A third possible explanation is that these techniques are not testing—or rather are not only testing—what we think they are testing. For example, there is compelling evidence that oVEMP reflects a specific muscle response to utricular stimulation (de Burlet 1924; Curthoys 2010, 2017; Manzari et al. 2010; Curthoys et al. 2011, 2014; Weber and Rosengren 2015), but this does not guarantee that the response is purely originating from the utricle. Since there are neural anastomoses within the vestibular nerve (such as Voit's nerve (Voit 1907; Gacek and Rasmussen 1961; Curthoys et al. 2014), which carries about 10% of saccular fibers into the superior division of the vestibular nerve), it is quite conceivable that the oVEMP response partly reflects input from other labyrinthine structures. As far as OT is concerned, there is evidence that cycloposition in at least some circumstances can be modulated by input from semicircular canals (Brandt and Dieterich 1994; Angelaki et al. 2002); it is predominantly, though not purely, a marker of otolith function.

Limitations, strengths, generalizability

There are several limitations to this study. The first is its retrospective design. The second is its relatively small sample size, yet our view is that the demonstration that just under half of the cases show concordant abnormalities of oVEMP and OT is sufficiently convincing of discordance between the two groups of results. The third is that the oVEMP and OCT were not performed simultaneously or at the same interval (from symptom onset) for each patient. Advantages of this study include that it is the first to compare directly the results of oVEMP and ocular cycloposition in a series of cases of

vestibular neuritis. These findings may not be generalizable to other unilateral vestibular lesions (e.g., labyrinthitis, vestibular schwannoma).

Conclusion

From a clinical standpoint, it is important to recognize that the results of oVEMP and ocular cycloposition reflect different functions of the utricle, and thus neither test can substitute for the other, even though their abnormalities often appear to overlap. Our data suggest that ocular cycloposition is abnormal less frequently than oVEMP in unilateral vestibular neuritis, but from a practical standpoint, assessment of ocular cycloposition has some clear advantages. When ocular cycloposition is studied with OCT, the test is very brief (a few seconds per eye), it does not require the use of a bright flash (unlike visible light retinal photography), it is not uncomfortable for the patient; even in miotic patients it does not require application of mydriatic eye drops it requires relatively little skill to perform the test and it is relatively operator independent, and its results are easy to interpret. These characteristics may make it feasible to deploy in an acute setting (such as an emergency room). Studying ocular cycloposition (whether by OCT or by visible light retinal photography) may also find a more common place in vestibular laboratories, as it objectively assesses a vestibular function that other tests (caloric testing, video head impulse testing, vestibular evoked myogenic potentials) do not characterize, and it does not rely on subjective responses from the patient (in contrast to SVH and SVV).

Future work should prospectively study a larger sample of patients, should perform oVEMP and OCT simultaneously, should perform the tests at a specific interval (or intervals) after symptom onset, and should include six-canal video head impulse testing systematically (to assess for possible contribution of canal input to ocular torsion).

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Compliance with ethical standards

Conflict of interest The author declares no conflict of interest.

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