Vestibular evoked myogenic potentials in children

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Background: The vestibular evoked myogenic potential (VEMP) test is a relatively new diagnostic tool that is in the process of being investigated in patients with specific vestibular disorders. Briefly, the VEMP is a biphasic response elicited by loud clicks or tone bursts recorded from the tonically contracted sternocleidomastoid muscle, being the only resource available to assess the function of the saccule and the lower portion of the vestibular nerve. Vestibular evoked myogenic potentials (VEMPs) are a useful and increasingly popular component of the neuro-otology test battery. These otolith-dependent reflexes are produced by stimulating the ears with air-conducted sound or skull vibration and recorded from surface electrodes placed over the neck (cervical VEMPs) and eye muscles (ocular VEMPs). VEMP abnormalities have been reported in various diseases of the ear and vestibular system, and VEMPs have a clear role in the diagnosis of superior semicircular canal dehiscence. However there is significant variability in the methods used to stimulate the otoliths and record the reflexes. This review discusses VEMP methodology and provides a detailed theoretical background for the techniques that are typically used. The review also outlines the common pitfalls in VEMP recording and the clinical applications of VEMPs in children.

Keywords: vestibular evoked myogenic potential, Children

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Introduction

Vestibular evoked myogenic potentials (VEMPs) are short-latency, vestibular-dependent reflexes that are recorded from the sternocleidomastoid (SCM) muscles in the anterior neck (cervical VEMPs or cVEMPs) and the inferior oblique (IO) extraocular muscles (ocular VEMPs or oVEMPs). They are evoked by short bursts of sound delivered through headphones or vibration applied to the skull. As these stimuli have been shown to preferentially activate the otolith organs rather than the semicircular canals, VEMPs are used clinically as measures of otolith function.

VEMPs can be recorded using standard evoked potential equipment with little modification and are therefore easily implemented in a range of clinical settings. As a result, VEMPs have become a standard component of the neuro-otology test battery over the past 20 years. However, there is a lack of consistency in recording procedures between clinics and differences in the quality of VEMP results reported in research papers. There is therefore a need for practical information about the basic requirements for VEMP recording as well as the theoretical basis underlying these requirements.

The cVEMP is a biphasic surface potential, with peaks at approx. 13 and 23 ms, recorded from electrodes arranged in a belly-tendon montage

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over the SCM muscle (Fig. 1). Cervical VEMPs were first described by Colebatch et al. (1994), who reported a click-evoked muscle reflex in the ipsilateral SCM, which was dependent upon vestibular, but not auditory, function. It scaled with stimulus intensity and the underlying SCM muscle activity and could be easily produced using standard evoked potential equipment and calibrated headphones. Intramuscular recordings later confirmed that the surface response is produced by a short inhibition of the SCM muscle (Colebatch and Rothwell, 2004). As air-conducted (AC) sound preferentially activates the saccule (Young et al., 1977, Zhu et al., 2014, Curthoys et al., 2016), cVEMPs evoked by this stimulus can be used as a test of saccular function.

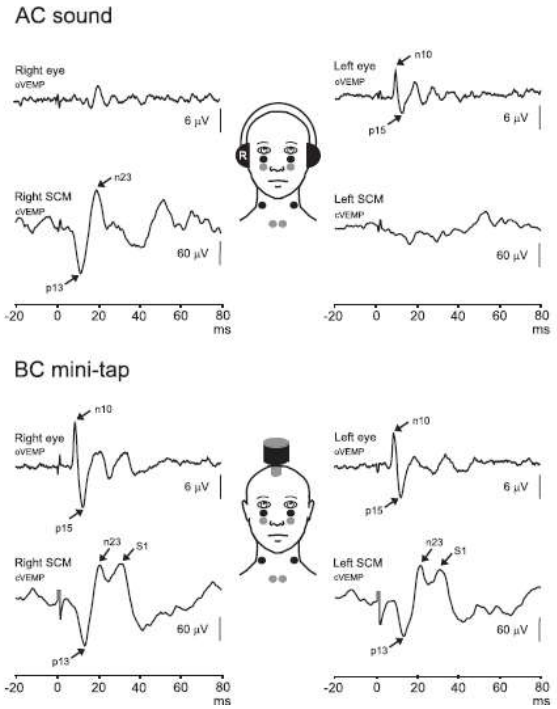

Fig. 1: cVEMPs and oVEMPs evoked by air-conducted (AC) sound and bone-conducted (BC) vibration in a normal volunteer. Typical electrode positions used to record oVEMPs and cVEMPs are shown bilaterally and consist of bipolar montages made up of active (black circles) and reference (grey circles) pairs. In the top panel, cVEMPs (lower traces) evoked by AC sound can be seen on the right side, i.e. ipsilateral to stimulation, while oVEMPs (upper traces) can be seen on the left side, contralateral to stimulation. In the bottom panel, VEMPs evoked by BC stimulation applied to the forehead are shown. Responses can be seen bilaterally, as BC stimulation activates vestibular afferents in both ears. cVEMPs evoked by BC stimulation can have additional peaks following the p13-n23 response (labelled S1 here), which are thought to be stretch reflexes.

Ocular VEMPs were first described a decade after the cVEMP (Rosengren et al., 2005, Iwasaki et al., 2007, Todd et al., 2007). They are evoked by the same stimuli but are reflexes of the extraocular muscles and thus represent activation of the vestibulo-ocular reflex instead of the vestibulo-collic reflex. The oVEMP originates in the inferior oblique muscle and is produced by a brief excitation of the muscle (Weber et al., 2012). The response consists of a biphasic surface potential with peaks at approx. 10 and 15 ms, beginning with a negativity (Fig. 1). Like the cVEMP, oVEMPs scale with stimulus intensity and muscle contraction and are recorded with surface electrodes placed on the cheeks underneath the eyes while the patient looks upwards. In contrast to the cVEMP, the oVEMP is a contralateral reflex, recorded from the eye opposite the stimulated ear. oVEMPs are used clinically to assess the function of the utricle. Evidence suggests that the oVEMP is produced by otolith afferents in the superior vestibular nerve (which contains all utricular afferents and a small number of afferents from the anterior saccule). Given this, and the fact that sacculo-ocular pathways are thought to be weak, the oVEMP is considered a test of utricular function (Govender et al., 2015).

Type and frequency

There is not one best VEMP stimulus, as there is significant variability in individual responses to stimuli of different shape and frequency (Taylor et al., 2012). AC sound is the most common VEMP stimulus modality. Clicks (0.1 ms square waves) were used in the initial report on cVEMPs and remain good stimuli, as they have a very fast onset and stimulate across a range of frequencies (approx. 1–4 kHz) (Burkard, 1984, Hood, 2015). Transmission to the saccule shows frequency tuning, with preferred frequency at approximately 500–1000 Hz (Young et al., 1977), and therefore AC tone bursts around these frequencies are also good stimuli. There are,

however, mean differences in tuning with age and between cVEMPs and oVEMPs, whereby higher frequencies produce larger reflexes in older subjects and for oVEMPs (Taylor et al., 2012a, Piker et al., 2013). Frequency tuning can also change in some inner ear diseases, such as Meniere's Disease (MD), whereby patients have larger responses to 1 kHz than 500 Hz stimulation (Rauch et al., 2004, Sandhu et al., 2012, Taylor et al., 2012c, Winters et al., 2012), and superior semicircular canal dehiscence (SCD), in which patients have broader tuning (Taylor et al., 2012c, Manzari et al., 2013).

Duration

Clicks are typically delivered with 0.1 ms duration, though can be longer. Likewise, tone bursts can be several milliseconds in duration. Increasing stimulus duration typically increases VEMP amplitude, as the total sound energy delivered to the inner ear is increased. However, the enhancement with increasing duration reverses after approx. 6–8 ms for cVEMPs and earlier for oVEMPs (Cheng and Murofushi, 2001a, Lim et al., 2013). In both cases, increases in duration must be tempered by decreases in intensity to keep the sound exposure of the cochlea within acceptable limits. We recommend stimulus durations of up to a maximum of 6 ms for tone bursts for clinical purposes, in part because some commercial systems used to perform VEMPs set minimum durations at this value. In addition to the trade-off between duration and intensity, there is a compromise related to frequency specificity, with longer stimuli providing greater specificity. For this reason stimuli up to 10 ms are sometimes used to test the tuning characteristics of the otolith organs, but are not recommended for routine use as they increase sound exposure. The same stimulus can be used for both cVEMPs and oVEMPs, however stimulus duration is a greater consideration for oVEMPs. As the reflex begins at approx. 6–7 ms, the latter part of long stimuli is likely to have little effect and stimulus artefact can obscure the initial wave due to the close proximity of the stimulation and recording sites.

Rise time

Rise time has a significant effect on the size and latency of the VEMP. The otolith organs may be sensitive to changes in acceleration over time (Curthoys et al., 2006, Jones et al., 2011) and thus VEMPs are larger and peak earlier if the onset of a stimulus (i.e. rise time) is short (Cheng and Murofushi, 2001b, Burgess et al., 2013). In fact, stimulus rise time is one of the major factors determining reflex latency and for this reason it is important to collect normal data for each stimulus.

Optimal stimulus parameters: Bone-conducted (BC) stimulation

Much less is known about the optimal stimulation characteristics for BC stimulation. The most important difference between AC and BC stimuli is that the latter is a bilateral stimulus. Healthy adults typically have BC cVEMPs and oVEMPs bilaterally, especially when stimulated in the midline of the skull. In patients with unilateral vestibular loss, the BC cVEMP is either absent on the affected side, or an inverted 'crossed' response is seen, with latency typically slightly earlier than the p13. The absence of a normal p13-n23 response in the ipsilateral SCM indicates loss of function. Likewise, for the BC oVEMP, patients with unilateral vestibular loss have oVEMPs opposite the normal ear but no response opposite the affected ear (as the reflex is contralateral). Thus the laterality of both reflexes allows clinical interpretation even though the stimulus activates both ears at once.

The initial report of BC cVEMPs described reflexes evoked by tendon hammer taps to the forehead (Halmagyi et al., 1995). Subsequent studies showed that tone-bursts delivered with a B-71 bone-conductor (Sheykholeslami et al., 2000, Welgampola et al., 2003) or electromechanical vibrator (Iwasaki et al., 2007) were also effective stimuli. BC stimulation has been more difficult to implement as existing evoked potential systems sometimes require modification to produce the stimulus. Taps are usually delivered with a triggered tendon hammer (or a standard tendon hammer modified with an accelerometer trigger) and require an option of an external trigger, while BC tone bursts usually require stronger amplification via an

additional external amplifier. The same principles of a fast rise time and short duration apply to BC stimuli, however sound exposure is no longer relevant. The perceived sound loudness is much lower for effective BC sounds compared to AC, indicating their greater effectiveness for stimulating vestibular compared to cochlear receptors (Welgampola et al., 2003).

Stimulus frequency

Frequency tuning for BC stimuli is lower than for AC stimulation, and reflexes recorded at or above 1000 Hz are usually small, particularly given that stimuli are usually matched across frequency using constant force (Sheykholeslami et al., 2001, Welgampola et al., 2003, Zhang et al., 2012, Curthoys et al., 2016). It is also more difficult to deliver efficient BC vibration to the skull above these frequencies. A 500 Hz tone burst is a popular stimulus, in part because it has been comprehensively studied in animals (Curthoys et al., 2012). This frequency also lies within the optimal output range of many bone-conductors and stimulators, as it is commonly used to test bone-conducted hearing. Lower frequencies, such as 125 or 100 Hz, especially when delivered over 4 or 5 ms respectively (exact half sine waves), produce similar head acceleration as that produced by a tendon hammer, and can be delivered in a more controlled manner and with different intensities.

Stimulus intensity

The otolith organs are very sensitive to skull vibration and thus the optimum stimulus intensity for clinical purposes is typically a compromise between the output capability of the stimulator and patient comfort. It is important to ensure that the stimulus produces good responses in most normal people before testing patients. It is possible to produce a bruise with overly vigorous BC stimulation, thus care should be taken in the force of stimulus delivery and number of repetitions. Bone-conducted stimuli should be calibrated in force level (FL). An effective stimulus for a B-71 bone-conductor at the mastoid using 500 Hz is approx. 135 dB pkFL (Rosengren et al., 2009). Skull accelerations of approx. 0.1–0.4 g (measured at the first acceleration peak) when measured at the mastoid are effective and typically used (Rosengren et al., 2009, Zhang et al., 2012, Taylor et al., 2014a). Tendon hammer taps are typically more variable and are operator-dependent, however they produce robust oVEMPs and are often the easiest form of BC stimulation to implement (Rosengren et al., 2011).

Stimulus location

Stimuli can be delivered to the mastoid or in the midline of the skull, usually over the forehead. Tendon hammer taps usually produce good cVEMPs and oVEMPs when applied to either site, though the results can be variable due to operator inconsistency. In contrast B-71 bone-conductors placed on the mastoid typically produce good cVEMPs but poorer oVEMPs (Rosengren et al., 2011), and this bone-conductor is difficult to attach firmly to the forehead. A stronger electromechanical vibrator, such as a 'minishaker' (model 4810, Brüel and Kjaer, Denmark) or V201 shaker (Ling Dynamic Systems, Royston, England), typically evokes good reflexes from either site. The 4810 has the advantage that its output is much less affected by loading conditions than the V201 (Colebatch JG, unpublished observations).

Both cVEMPs and oVEMPs evoked by BC stimulation are sensitive to the direction of skull acceleration produced by the stimulus (Brantberg and Tribukait, 2002, Todd et al., 2008a, Rosengren et al., 2009, Jombik et al., 2011). Responses can change polarity and/or latency with different sites of stimulation. The effects are much greater for taps and low frequency tone bursts, but are still present with 500 Hz stimuli (Cai et al., 2011). When delivered to the anterior forehead around the hairline, stimuli that begin with acceleration toward the skull (as with a standard tenon hammer tap) produce earlier responses than those that begin with acceleration away from the skull, but the effects for other midline sites differ (Govender and Colebatch, 2017, Govender and Colebatch, 2018). When delivered to the mastoid in the interaural direction and with the stimulus accelerating towards the skull, the response on the side of the major projection (ipsilateral for

cVEMPs, contralateral for oVEMPs) has the earlier response.

Apart from the above systematic effects of stimulus location, BC cVEMPs and oVEMPs are sometimes sensitive to small variations in vibrator placement. We suggest shifting the vibrator and trying nearby locations if BC VEMPs are very small or absent.

cVEMP and oVEMP reflex measurement

Amplitudes and latencies are measured at the response peaks, which occur at approx. 13 and 23 ms for the cVEMP and 10 and 15 ms for the oVEMP, depending on the stimulus. The difference between the peak amplitudes is taken to give the PP amplitude. For cVEMPs, if a measure of SCM muscle activity is available, a 'corrected amplitude' can be calculated to take the muscle contraction strength into account. This is done by dividing the PP amplitude by the measure of contraction strength to form a (unit-less) ratio. For oVEMPs, some laboratories prefer to use only n10 amplitude. To compare the two ears, the interaural asymmetry ratio (IAR) is calculated using the Jongkees formula ((right − left)/(right + left)) (or its absolute value, which will have a different normal range) either on the raw PP amplitude or on the amplitude ratio. If threshold is measured, it is reported in dB.

It is very important to have at least some normative data collected locally, in order to estimate the upper and lower limits for amplitude, latency and symmetry. The latency parameter is particularly affected by stimulus shape and rise time. (Rosengren et al., 2011)

Asymmetries in VEMP amplitude are usually readily interpretable. Except in third mobile window disorders and early Meniere's disease (Young et al., 2002), the side with the smaller amplitude is usually the abnormal side. Bilateral vestibular loss is more difficult to detect, as cVEMPs and oVEMPs can be very small or absent in some normal people. It is reasonable to set a lower limit of normal amplitude at the 5th percentile of normative values, as a means of detecting abnormal VEMPs in patients with bilateral vestibular loss (Agrawal et al., 2013, Tarnutzer et al., 2018).

Equipment required for recording VEMPs

Most evoked potential systems capable of recording brainstem auditory evoked potentials are capable of recording VEMPs, but are not ideal. The common limitations are that only clicks are available, no calibration in SPL is given, the maximum stimulus intensity is limited, and rectified EMG levels cannot be measured. BC stimulation through an electromechanical vibrator, such as a minishaker, requires an additional dedicated power amplifier. Recent research suggests that portable, smart phone-based devices may become available in time, providing AC and tendon hammer (impulsive) stimuli (MacDougall et al., 2018).

For research applications, a suitable amplification system, interface and collection programs are required for recording. Stimulation requires calibrated headphones for AC sound (and output limits to prevent inadvertent overstimulation and damage to hearing), a modified tendon hammer with a sensitive trigger or electromechanical vibrator (optional but desirable) for BC stimulation, and suitable power amplifiers.

Clinical application of VEMPs

cVEMPs and oVEMPs are now widely used to test otolith function in patients with vertigo and imbalance. They are used to reveal loss of otolith function, i.e. in conditions where damage to the inner ear, vestibular nerve, or central vestibular pathways occurs, such as in Meniere's disease (MD), vestibular neuritis (VN), vestibular schwannoma (VS) or stroke. They are also commonly used to detect enhancement of otolith activation by sound and vibration, such as in third mobile window disorders like SCD. Like other evoked potentials, VEMPs are also sensitive to slowing of conduction along the neural pathways, and thus latency prolongation can be another useful test parameter. Caution is warranted in interpreting latency delay, as it can also be caused by technical factors, such as electrode placement. VEMP abnormalities should be interpreted in light of measures of semicircular canal function and hearing, taking

into account the potential false positive rate of each VEMP.

VEMPs in acute vestibular syndrome (AVS)

A sudden disabling episode of spontaneous vertigo lasting one or more days could represent vestibular neuritis, an innocuous self-limiting illness, or posterior circulation stroke (PCS), a life threatening cause. VN is associated with distinctive physical signs and vestibular test abnormalities, while PCS is accompanied by diverse physical signs and test profiles. Thus in AVS, it is common to first seek the cardinal features of VN and, if they are absent, then investigate for stroke.

Acute VN can affect the superior, inferior or both divisions of the vestibular nerve or even the ampullary nerves individually (Walther and Blödow, 2013, Magliulo et al., 2014, Taylor et al., 2016). The superior vestibular nerve demonstrates the highest prevalence of abnormalities, and the whole nerve is affected in 50–55% of patients with VN (Magliulo et al., 2014, Taylor et al., 2016). An absent or reduced AC and BC oVEMP in the presence of a preserved AC cVEMP is a common finding in VN (Fig. 10). The prevalence of oVEMP abnormalities is close to ∼70% compared to ∼40% for the cVEMP (Taylor et al., 2016). Labyrinthitis and labyrinthine infarction can present with sudden sensorineural hearing loss and vertigo. Some patients will demonstrate vestibular test abnormalities that map to the common cochlear artery, which supplies the cochlea, saccule and posterior canal. In a case series of 27 subjects, while the prevalence of posterior canal dysfunction was high (74%), prevalence of AC cVEMP asymmetry (30%) was lower than expected, probably since the participants were not tested acutely (Pogson et al., 2016).

Vestibular evoked myogenic potentials in children

Most vestibular disorders in infants and young children manifest not as vertigo or dizziness, but as balance problems and/or developmental delay of motor milestones. Early identification of such disorders is necessary for early intervention. [1] It is important to consider a time-efficient, noninvasive, accurate, and comfortable test battery for vestibular assessment that is appropriate for children of all ages. However, selecting tests that are appropriate for use with the pediatric population is a great challenge. Many studies have focused mainly on the application and adaptation of adult tests such as video-nystagmography, computerized dynamic posturography, rotary chair, and cervical vestibular-evoked myogenic potentials (cVEMPs). Typically, children in these studies were aged 5 years or older, with the exception of the new normative cVEMPs data, wich covers age ranges from a few days through the teen years. (Ibraheem et al., 2018)

Cervical vestibular-evoked myogenic potentials testing is applicable to all subjects, and is gradually becoming a part of the standard vestibular assessment in many clinics. It is a short-latency electromyographic (EMG) response evoked mainly by loud acoustic stimuli. Sound-induced vibrations of the perilymph within the saccule are thought to give rise to the cVEMPs. The saccular afferent conduction passes through the inferior vestibular nerve to the medial vestibular nucleus. The vestibulo-collic tract then carries an inhibitory response via the motor neurons of the 11th cranial nerve to the cervical flexor motor neurons. The cVEMPs are measured from the ipsilateral sternocleidomastoid (SCM) muscle while the muscle is activated. (Ibraheem et al., 2018)

Adaptations of adult cVEMPs have been previously described for use with children. However, these have not been widely used on either a research or clinical basis. One procedure is to standardize the level of SCM muscle contraction by target monitoring of EMG activity using an extra neck electrode. Applying this electrode to children is not feasible because of their small necks, but it is possible to calculate the asymmetry ratios or the normalized amplitude from raw amplitude measures. Other cVEMPs adaptations include placing the child on a parent's lap, having the child focus on a cartoon film to maintain head turn for muscle contraction, positioning the child for simultaneous bilateral recording, using 500 Hz stimuli to obtain a more robust waveform, and

continuous positive reinforcement. (Ibraheem et al., 2018)

Vestibular evoked myogenic potentials (VEMP) are commonly used to assess both portions of the vestibular nerve and otolith organs (1–5). In adults, VEMPs can be reliably elicited with either air- or bone-conducted stimuli (6); however, similar studies assessing the reliability of VEMPs in children have not been published. The VEMP is a muscle potential elicited in response to high intensity stimuli (1). The cervical VEMP (cVEMP) is a short-latency inhibitory response recorded ipsilaterally from the contracted sternocleidomastoid (SCM) muscle and provides information about saccule and inferior vestibular nerve function (1). The ocular VEMP (oVEMP) is an excitatory response recorded contralaterally from the inferior oblique muscle and provides information about utricle and superior vestibular nerve function (MacDougall et al., 2018).

VEMP responses are not dependent on auditory sensitivity and can be recorded in individuals with sensorineural hearing loss .However, conductive hearing loss can reduce or eliminate air-conduction VEMP responses due to attenuation of the stimulus reaching the otoliths. Therefore, the use of bone-conduction stimuli can assist in evaluating otolith function in populations with middle ear issues. Various methods of bone-conduction, including bone oscillators, mini-shakers and reflex hammers, have been shown to effectively evoke VEMP responses. Reflex hammer VEMP generally result in shorter latencies and larger amplitudes, likely due to more effective activation of vestibular afferents. (Pogson et al., 2016).

Studies investigating the reliability of VEMPs in children have not been explored, based on the authors' literature search. Several factors could impact reliability of VEMP responses in children, including maintaining effective SCM contraction during cVEMP and sustainment of up-gaze during oVEMP testing. We hypothesized children would have more difficulty maintaining adequate SCM contraction, and therefore, demonstrate greater cVEMP variability than adults. In oVEMP, children may not be able to sustain up-gaze due to inattention. One strategy utilized in our laboratory is to mount an iPod at 30-degrees up-gaze and have children watch a video. However, an alternative method is to obtain oVEMP with eyes closed .oVEMP can be obtained with eyes closed because of Bell's Phenomenon, the eyes roll upward and inward with closure, allowing for recording from the contracted inferior oblique muscle. Bell's Phenomenon is present in 90–97% of individuals. The reliability of eyes-closed oVEMP has not been explored in adults or children; however, we hypothesized that oVEMP variability may improve in children if completed with eyes closed. (Pogson et al., 2016).

Several other variables can affect VEMP reliability. Variations in electrode placement can impact amplitude and latency. Ear canal volume can affect stimulus intensity (i.e. higher sound pressure levels with smaller ear canal volumes) and thus affect VEMP amplitude. Increased neck length and thickness has been correlated with increased cVEMP latency. Similarly, we hypothesize that external anatomic landmarks might correlate with oVEMP (i.e., the inter-mastoid distance, which can be used to infer the inter-utricular distance. There is limited information regarding the reliability of vestibular testing in children, including VEMP testing. (Pogson et al., 2016).

Conclusion

Air-conducted c- and oVEMPs, and impulse hammer cVEMPs are reliable tests of otolith function in normal control children. EC-oVEMP were less reliable compared to EO-oVEMP and resulted in a large number of absent responses; therefore, EC-oVEMP is not considered a reliable condition. However, when a bone-conducted stimulus is needed (i.e., in children with middle ear issues), impulse hammer oVEMPs can be used. When using an impulse hammer in children, EC-oVEMP resulted in better reliability compared to the EO condition; however, this trend was not present for adults. Undiagnosed and untreated vestibular dysfunction can have a significant impact on children's motor development and academic difficulties, due to the inability to maintain stable gaze. The potential risks of vestibular dysfunction warrant

the importance of effective testing and diagnosis in children.

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