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Main Article

Vestibular-evoked myogenic potentials and caloric stimulation in infants with congenital cytomegalovirus infection

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Abstract

Background: The influence of congenital cytomegalovirus infection on cochlear function has been well recognised; however, its impact on the vestibular system in infants has not been examined. The purpose of the present study was to evaluate vestibular function in a group of infants, using caloric stimulation tests and vestibular-evoked myogenic potential measurements.

Materials and methods: Vestibular-evoked myogenic potentials and auditory brainstem responses were recorded and caloric stimulation was performed in 66 infants aged three months, comprising 40 healthy controls and 26 infants with congenital cytomegalovirus infection.

Results: No reaction to caloric stimulation was elicited from 16 examined ears, no vestibular-evoked myogenic potentials were recorded from 12 ears, and profound sensorineural hearing loss was diagnosed in eight ears. Pathological results were observed predominantly in infants with symptoms of intrauterine congenital cytomegalovirus infection present at birth.

Conclusions: In infants with clinical symptoms of congenital CMV infection present at birth, abnormal vestibular test results occurred more frequently than abnormal auditory brainstem response results. Vestibular organs should be routinely examined in individuals with congenital cytomegalovirus infection.

Key words: Inner Ear; Vestibule; Saccule; Caloric Tests; Infants; Cytomegalovirus

Introduction

Congenital cytomegalovirus (CMV) infection, like that of most of the group of organisms including toxoplasmosis, rubella, CMV, herpes virus and others, causes mild maternal morbidity but has serious fetal consequences. Cytomegalovirus is one of the herpesviridae, known for their potential for latency and reactivation.[1] Cytomegalovirus may cause damage to cochlear outer ciliary cells, and is a major cause of sensorineural hearing loss.[2–6]

Although many infants with symptomatic congenital CMV infection develop hearing loss, only a minority have symptoms of inner-ear damage present at birth.[4,5] Further CMV-induced damage to the inner ear, due to enlargement of the vestibular aqueduct, may occur in the first few months of life.[4,6] It has been determined that petechiae and intrauterine growth retardation observed at birth independently predict hearing loss in infants with congenital CMV infection.[5]

Sensorineural hearing loss in infants with congenital CMV infection is well recognised; however, there is little clinical evidence of CMV causing damage to the vestibular system. Although there is a strong supposition that CMV infection can influence vestibular function in infants,[7] routine infant inner-ear examination does not include vestibular tests.

Vestibular-evoked myogenic potentials, which occur in cervical muscles after intense acoustic stimulation of the ear, are a polysynaptic response of otolith-vestibular nerve origin.[8–11] This reflex originates in the saccule, the afferent pathway of which is the inferior vestibular nerve, and the efferent pathway of which is the vestibulospinal tract. Averaging these muscular responses allows vestibular-evoked myogenic potentials to be recorded.

Since 1992, when Colebatch and Halmagyi first recorded vestibular-evoked myogenic potentials, this test has become a diagnostic tool enabling evaluation of the integrity of the sacculocollic reflex, shedding new light on vestibular testing and on possibilities of evaluating the otolith organ's function.[10,12,13]

Following monaural acoustic stimulation (usually), vestibular-evoked myogenic potentials are measured on the sternocleidomastoid muscle ipsilateral to the stimulation, or bilaterally.[10] The responses consist of positive and negative successive waves (pI-nII),

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with latency values in adults of about 13 and 23 msec, respectively.[9,11,13,14] The latencies are shorter in infants, being about 7 and 12 msec, respectively,[15,16] most probably due to the lack of inhibition in the reflex pathways. The vestibular-evoked myogenic potential amplitude depends on stimulus intensity and muscular tension, and is less reliable than the latencies of the waves.[17]

Vestibular-evoked myogenic potentials can be evoked by short tone bursts or by clicks.[8,18] Short tone bursts are most effective in eliciting a consistent vestibular-evoked myogenic potential response in adults.[19]

Caloric stimulation is difficult to perform in infants due to lack of cooperation of the subject with the examiner. It is, nevertheless, the only reliable diagnostic tool used for assessing the function of the lateral semicircular canal in this age group, as the responses to caloric stimulation mature rapidly during the first three months. Furthermore, three months is the optimal age for caloric stimulation testing, according to Eviatar and colleagues.[20,21] The response depends on the excitability of the receptors (slow phase of nystagmus) that are present at birth, on the neurological mechanisms of initiation of the fast phase of nystagmus, and on the maturation of inhibitory systems.[20,21] In healthy infants, the vestibular pathways are anatomically and physiologically mature at birth.[20,22–24] In infants, the slow phase, which is vestibular, can produce tonic deviation of the eyes in the appropriate direction even before the fast phase is functional.[20,21] The test must be performed in infants with great care, and requires a strong caloric stimulus – cold water.[22]

The aim of the current study was to determine the condition of different parts of the inner ear in infants with congenital CMV infection, using caloric stimulation and recordings of vestibular-evoked myogenic potentials and auditory brainstem responses (ABRs).

Materials and methods

Sixty-six infants aged three months were included in the study. These included 40 healthy infants (13 girls and 27 boys, 80 ears), who were examined as controls. Twenty-six infants with congenital CMV (14 girls and 12 boys, 52 ears) were also included, on condition that: blood tests were positive for CMV immunoglobulin (Ig) G and IgM antibodies in the mother; and the infection was confirmed in the newborn by urinary viral isolation after birth.

Subjects treated with ototoxic drugs (aminoglycosides or furosemide) and infants with evidence of intraventricular haemorrhage confirmed on cerebral ultrasound were excluded from the study. All infants with external- and middle-ear pathology were also excluded.

Infants with congenital CMV infection were subdivided into two subgroups: 10 infants with clinical symptoms of CMV intrauterine infection present at birth; and 16 asymptomatic infants. The clinical symptoms at birth included: presence of intrauterine growth retardation (four infants), petechiae, hepatosplenomegaly and/or hepatitis (six), thrombocytopenia (four), and intracerebral calcifications (six). Congenital or acquired infections with toxoplasmosis, rubella or herpes virus were excluded in all examined individuals.

Cerebral ultrasound, otoscopy, tympanometry, click-evoked otoacoustic emission (OAE) testing, ABR testing and cold water caloric stimulation were performed in each infant at the beginning of the examination. Caloric testing was performed with 20 ml of water (temperature 20ºC) introduced into the external ear canal for 20 seconds.

Evoked nystagmus was observed directly, unaided by instrumentation. The latency and duration of the response were measured. Normal nystagmus reaction to caloric stimulation, obtained in the healthy individuals, began after 5–15 sec of latency and lasted 60–70 sec. Significant weakening of the response was diagnosed when its latency and/or duration differed from this pattern by more than 30 per cent.

Auditory brainstem response waves were recorded using a Centor-C ABR machine (Racia-Alvar, France) after exposure to broad-band 2000–4000 Hz clicks.

All vestibular-evoked myogenic potential testing was performed with the same machine. Vestibular-evoked myogenic potentials were averaged from 75 responses to an air-conducted, frequency 500 Hz, 90 dB SPL tone burst stimulating one ear, with no masking noise on the other side, with a stimulation repetition rate of 5 Hz, a rise-and-fall time of 1 msec, and a plateau time of 2 msec. Surface electromyographic activity was recorded in supine neonates from symmetrical sites over the upper half of each isometrically contracting sternocleidomastoid muscle. Contraction of the muscles was facilitated by bending the infant's head slightly backwards and holding it in this position, which provoked a relatively strong reflex muscle contraction, making it possible to record the responses. A reference electrode was placed over the upper sternum. Electromyographic activity was recorded under the following three conditions: no muscle contraction plus no acoustic stimulation; muscle contraction plus no acoustic stimulation; and muscle contraction plus acoustic stimulation.

The vestibular-evoked myogenic potential latency measurements obtained from CMV-infected infants were compared with those from healthy controls. Spearman's correlation coefficients were calculated to determine whether there was a significant relationship between the presence of normal ABR results, vestibular-evoked myogenic potential results and caloric responses. The Mann–Whitney U test was used to determine whether there were significant differences between the distribution of measurements obtained in healthy versus CMV-infected infants. The chi-square test was used in order to compare the frequencies of pathological results in each CMV-infected infant subgroup. Spearman's correlation coefficients were used to determine whether there was a significant relationship between the presence of OAEs and ABR-determined hearing threshold values.

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Prior to the examination, the parents of each infant gave their informed consent for their child's participation in the study. The research plan was approved by the local medical ethics committee.

Results and analysis

During clinical examination, no pathological findings were observed in any infant.

Consistent, unilateral, biphasic vestibular-evoked myogenic potentials, the first positive and the second negative (pI, nII), were elicited in all 80 ears in the healthy infants and in 40 ears in the CMV-infected infants (Figure 1). No vestibular-evoked myogenic potentials were recorded from 12 ears of CMV-infected infants symptomatic at birth.

In all controls and in 36 ears of CMV-infected infants, the responses to caloric stimulation were normal. In 16 ears of CMV-infected infants, caloric responses were absent. Profound hearing loss was diagnosed in only four CMV-infected infants (eight ears) (Tables I, II and III). In eight ears of CMV-infected infants symptomatic at birth, no response to acoustic or caloric stimulation was recorded. Caloric responses were disturbed more frequently than otolith functions.

There were no statistically significant differences between vestibular-evoked myogenic potential wave I and II latency measures, comparing CMV-infected infants and controls. Statistically significant correlations were found between the presence of normal vestibular-evoked myogenic potentials and normal caloric responses ($p < 0.001$, $r = 0.8$), and between the presence of normal hearing thresholds on ABR examination and normal vestibular-evoked myogenic potentials ($p < 0.001$, $r = 0.7$). There was also a

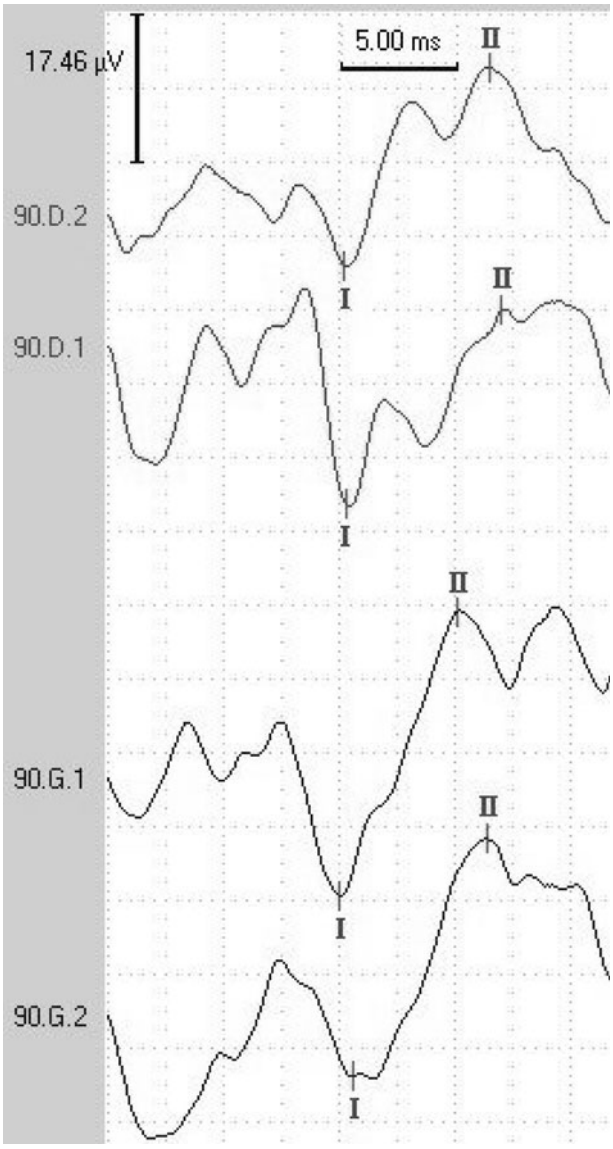

FIG. 1

Vestibular-evoked myogenic potentials recorded in a healthy infant. D.2 = waveform recorded after ipsilateral acoustic stimulation of right ear; D.1 = waveform recorded after contralateral acoustic stimulation of right ear; G.1 = waveform recorded after ipsilateral acoustic stimulation of left ear; G.2 = waveform recorded after contralateral acoustic stimulation of left ear

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TABLE I

VEMP WAVES I AND II LATENCY VALUES IN CMV-INFECTED AND HEALTHY INFANTS

Pt group	Latencies (mean (SD); msec			
	Ipsilateral wave		Contralateral wave	
	I	II	I	II
Controls	8.3 (1.7)	13.5 (2.5)	8.5 (1.8)	13.8 (2.5)
CMV	8.5 (1.3)	13.8 (1.5)	8.6 (1.2)	13.7 (1.9)

VEMP = vestibular-evoked myogenic potential; CMV = cytomegalovirus; pt = patient; SD = standard deviation

statistically significant correlation between the presence of a normal hearing threshold and a normal caloric response ($p < 0.001$, $r = 0.9$). The caloric test was the most sensitive indication of CMV affecting the inner ear, followed by vestibular-evoked myogenic potentials and then ABR ($p < 0.001$). Otoacoustic emissions were absent in all ears with an elevated hearing threshold ($p < 0.001$, $r = 1.0$).

Discussion

Positive blood isolation of CMV at birth provides an approximately 93 per cent certainty of in utero infection.[25]

It is crucial to perform otoscopy and tympanometry prior to eliciting vestibular-evoked myogenic potentials, as conductive hearing loss makes recording impossible; the patency of the external ear canal must also be confirmed prior to performing caloric irrigation.[26]

Elicitation of sternocleidomastoid muscle contraction is necessary in order to obtain a vestibular-evoked myogenic potential measurement; therefore it is preferable that the patient under examination should collaborate with the examiner. However, bending an infant's head slightly backwards and holding it in this position evokes relatively strong reflex muscle contractions, which makes recording of the responses possible.

Waveforms obtained after acoustic stimulation with no muscle contraction must be compared with responses recorded after acoustic stimulation with muscle contraction, in order to differentiate between vestibular-evoked myogenic potentials and muscle artefacts, and between true vestibular-evoked myogenic potentials and auditory brainstem responses recorded on the neck muscles.[11] The acoustic stimulus characteristics used in this study to elicit vestibular-evoked myogenic potentials were consistent with the current stimulation pattern.[27] The characteristics of responses to stimulation may sometimes vary among individuals.[20,22–24] This explains the relatively high standard deviation values obtained for vestibular-evoked myogenic potential waveform latencies. Vestibular-evoked myogenic potential amplitude values were not analysed in the current study, as in infants the conditions for recording vestibular-evoked myogenic potentials are difficult and the results may vary depending on the intensity of sternocleidomastoid muscle contraction elicited.[15,17,28]

TABLE II

TEST RESULTS FOR INFANTS WITH CONGENITAL CMV INFECTION

Test & response	Ears (*n* (%))
Caloric stim	
Normal	36 (69.2)
Weak	0
None	16 (30.8)
Hearing threshold	
<20 dB HL	44 (84.6)
20–80 dB HL	0
>80 dB HL	8 (15.4)
VEMP	
None	12 (23.1)
Stim of SCCs & otolith organ	
No response	8 (15.4)

CMV = cytomegalovirus; stim = stimulation; VEMP = vestibular-evoked myogenic potentials; SCC = semicircular canal

TABLE III

TEST RESULTS FOR CMV-INFECTED INFANT SUBGROUPS

Test & response	CMV-infected infants (ears; *n*)	
	Asympt	Sympt*
ABR		
Normal	32	12
20–80 dB	0	0
>80 dB	0	8
Caloric stim		
Normal	28	8
Weak	0	0
Absent	4	12
VEMP		
Normal	32	8
Absent	0	12

*Clinical symptoms of congenital cytomegalovirus (CMV) infection present at birth. Asympt = asymptomatic; sympt = symptomatic; ABR = auditory brainstem response; stim = stimulation; VEMP = vestibular-evoked myogenic potentials

- **Although the influence of congenital cytomegalovirus (CMV) infection on cochlear function has been well recognised, its impact on the vestibular system in infants has not been examined**
- **In this study, vestibular function was assessed in three-month-old CMV-infected infants, using caloric and vestibular-evoked myogenic potential testing**
- **Vestibular dysfunction was observed more frequently than sensorineural hearing loss, suggesting that vestibular tests should be undertaken in this group of infants**

The fact that caloric responses were more frequently disturbed than vestibular-evoked myogenic potentials may have been due to suboptimal

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stimulation of the external ear canal and/or to the nystagmus study technique, considered by the author to be optimal in this group of patients. The results of caloric stimulation performed in infants have been previously reported, but those for congenitally CMV-infected infants have not been analysed.[20,21,29] Vestibular-evoked myogenic potentials have been recorded in infants by Sheykholesami *et al.*[16] and Zagólski *et al.*[15,28] The current paper is the first to present the results of caloric testing and vestibular-evoked myogenic potential measurement in infants with congenital CMV infection.

The strong correlation observed between caloric testing and vestibular-evoked myogenic potential results suggests that the influence of CMV infection on the inner-ear receptor cells causes damage the receptor cells of both the saccule and the lateral semicircular canal. In the present group of CMV-infected infants, there was a relatively high incidence of profound sensorineural hearing loss and no reactivity to vestibular receptor stimulation; this could suggest that intrauterine CMV infection causes damage to a large number of inner-ear receptor cells. Therefore, in the current study, there were no ears with weakened reactions to vestibular stimulation nor with elevated (20–80 dB HL) hearing thresholds. The higher incidence of complete lack of inner-ear functions in subjects with clinical symptoms of intrauterine CMV infection present at birth confirms the supposition that occurrence of CMV-induced brain damage and psychomotor retardation can correlate with inner-ear dysfunction. Because most infants with congenital CMV infection are asymptomatic at birth, these children are unlikely to be recognised as being at risk of sensorineural hearing loss, and thus will not receive further hearing evaluations in order to detect hearing loss and/or vestibular disorders.[30]

These findings suggest the necessity of thorough, routine examination of both hearing and balance organs in infants with congenital CMV infection.

Conclusions

The frequency of vestibular dysfunction was found to be greater than that of sensorineural hearing loss in three-month-old infants with congenital cytomegalovirus infection. The vestibular organs should be routinely examined in such infants.

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