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Impact of congenital cytomegalovirus infection on vestibular dysfunction and hearing outcomes in a cohort of children

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This study aims to evaluate long-term vestibular function and hearing outcomes in a cohort of children with congenital cytomegalovirus infection (cCMV) using a comprehensive battery of vestibular and hearing tests, and possible relationships between vestibular and cochlear damage and relevant clinical presentation variables of cytomegalovirus (CMV) infection. A prospective cohort study was carried out from June 2016 to December 2023 and included 40 children affected by cCMV. Our sample was composed by 35% males and 65% females, with age at first vestibular assessment ranging from 3 to 8 years old, and 30% (12) were symptomatic at birth. All patients received their diagnosis during the neonatal period, with none diagnosed retrospectively through dried blood spots. The median follow-up period was 5.3 years (ranging from 4.6 to 6.0). Comparing children with and without symptoms related to CMV, the presence of hearing loss (50% vs. 0.0%, $p = 0.0002$), psychomotor delay (25% vs. 0.0%, $p = 0.024$) and vestibular dysfunction (VD) (66.7% vs. 17.9%, $p = 0.0075$) were significantly increased in symptomatic patients. The VD was confirmed with a reduced gain of the lateral semicircular canals (LSCC) at the video head impulse test (vHIT) (58.3% vs. 17.9%, $p = 0.021$), and with the absence of response at cervical vestibular evoked myogenic potentials (cVEMPs) (54.5% vs. 3.7%, $p = 0.0009$). Comparing children with and without VD, we found a significant presence of reduced LSCC gain during the vHIT (93.3% vs. 0.0%, $p < 0.0001$), of an exclusive alteration in cVEMPs (61.5% vs. 0.0%, $p < 0.0001$), of hearing loss (46.2% vs. 0.0%, $p = 0.0004$), of patients with symptoms related to cCMV at birth (61.5% vs. 14.8%, $p = 0.0075$), of pathological neuroimaging at onset (61.5% vs. 7.4%, $p = 0.0006$), presence of antiviral therapy (61.5% vs. 11.1%, $p = 0.0017$) and positive viremia at onset (100% vs. 63%, $p = 0.018$). Finally, about time of maternal CMV infection the first trimester was associated to children with VD, while the third trimester to children without VD. cCMV infection can involve the entire inner ear: vestibular function seems to be more affected than cochlear function. Therefore, vestibular evaluation should be included in the audiological work up and follow-up in children with cCMV.

Keywords Cytomegalovirus, Congenital cytomegalovirus, Children, Vestibular dysfunction

Abbreviations

ABR	Auditory brainstem responses
cCMV	Congenital cytomegalovirus infection
CMV	Cytomegalovirus
cVEMPs	Cervical vestibular evoked myogenic potentials
IQR	Interquartile interval
PCR	Polymerase chain reaction
LSCC	Lateral semicircular canal
SD	Standard deviation
SNHL	Sensorineural hearing loss

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TEOAEs	Transient evoked otoacoustic emissions
US	Ultrasound
VD	Vestibular dysfunction
vHIT	Video head impulse test

CMV is the most common cause of congenital viral infection globally[1]. The estimated pooled overall prevalence rate of cCMV is 0.67%, ranging from 0.48% in high-income countries to 1.42% in low/middle-income countries[2]. Approximately 10% of congenitally infected newborns are termed "symptomatic" because they present one or more clinically observable abnormalities at birth, which include microcephaly, abnormalities at neuroimaging, jaundice, hepatosplenomegaly, petechiae, hearing loss, and chorioretinitis[3]. Most children with cCMV do not develop any consequences related to the infection. However, moderate to severe long-term impairment is diagnosed in almost 25% of infected children considered as a whole[4] and this prevalence is even higher among those who are symptomatic at birth (50–70%)[5,6], frequently presenting as sensorineural hearing loss (SNHL)[7–10]. Moreover, the main predictor of long-term sequelae is a maternal infection in the first trimester (< 14 weeks of gestational age), while no long-term sequelae are reported in those infected in the second or third trimester[11].

In recent years, vestibular and balance dysfunctions have been reported in children with symptomatic and asymptomatic cCMV infection at birth, both in those with and without hearing loss, as summarized by Shears et al.[9]. cCMV can have an impact on both the semicircular canals and the otolith function[12–14], resulting in a vestibular loss that may be severe, with variable onset and clinical progression over time[15,16].

The cochlear and posterior labyrinth tropism of CMV has been previously assessed in histopathological studies. In fact, CMV can cause virus-induced labyrinthitis, impacting both auditory and vestibular structures[17–20]. However, it is noteworthy that our understanding of cCMV-induced VD may currently be underestimated due to several factors, such as diagnostic challenges and the absence of specific guidelines governing the appropriate conduct of vestibular assessments in pediatric cases of cCMV.

As vestibular input is fundamental for appropriate early motor development, timely detection of vestibular loss could be crucial in helping children achieve their maximum potential. Indeed, the dysfunction of the vestibular system, leading to delays in gross motor skills, can potentially contribute to learning challenges and other neurodevelopmental disabilities[21]. However early detection of vestibular deficits is also difficult in young children due to their lack of appropriate language to indicate vestibular symptoms.

Nevertheless, routine examination for inner ear pathologies in infants predominantly centers around traditional audiological monitoring, with infrequent inclusion of vestibular assessments. Few data are currently available on the VD, therefore case–controlled longitudinal studies are desirable in order to characterize vestibular impairment and determine the efficacy of early interventions.

The aim of this study is to assess the long-term vestibular function and hearing outcomes in a cohort of children with cCMV using a comprehensive battery of vestibular and hearing tests. The primary objective is to determine the occurrence of vestibular dysfunction (VD) as a symptom in patients with cCMV. The secondary objective is to explore the association between relevant clinical variables of cCMV infection and the presence of VD in these children. The insights in the characteristic of VD in cCMV are important to schedule an appropriate follow up program.

Materials and methods

This was a prospective cohort study carried out at Specialized Perinatal Infection Unit of the University Federico II of Naples, in which we enrolled all infants and children with cCMV. The multidisciplinary team includes specialists from Neonatology, Maternal–Fetal Medicine, Pediatric Infectious Diseases, and Pediatric Audiologists dealing with the mother and infant dyad, focusing on vertically transmitted infections throughout the Campania Region. Serology examinations were performed by the local specialized reference laboratory. In this study, we stratified our sample population based on the presence or absence of vestibular dysfunction associated with CMV infection and conducted a comparative analysis. In this case the children had an appropriate follow up program started in 2014 and including into range [3.3. 8.7] years with mean of 5.4 years and 1.1 years of standard deviation, considering overall the sample. Particularly, this study started in 2016 and had a follow-up program that started in 2014, because it included one patient, with follow-up started in 2014, and four patients, with follow-up started in 2015.

Additional analyses were obtained by demographic and clinical data collected at inclusion, all audiological parameters, symptoms related to cCMV and data concerning mothers and pregnancy. Finally, all data collected were stored in electronic clinical records at the referent Operative Unit. Table 1 shows the information obtained on overall sample.

Study population

The universal neonatal screening for CMV is not offered in Italy, while the search of CMV DNA is performed in case of known or suspected maternal CMV infection during pregnancy and/or in case of symptoms in the neonatal period. In our cohort congenital infection was defined by viral DNA detection in urine using a polymerase chain reaction (PCR) assay within the first 3 weeks of life. When cCMV infection was suspected in older children, a retrospective diagnosis was made through PCR evaluation of dried blood spots[3]. At the time of enrollment, a blood sample was also collected to determine the presence of viremia.

Maternal CMV infection was categorized by analyzing maternal and newborn hospital records, as follow[22]: *primary infection* in case of demonstrated seroconversion during pregnancy or presence of CMV low-avidity IgG and specific IgM in the first trimester of gestation; *non-primary infection* in case of presence of IgG before pregnancy or IgG without IgM within the first trimester of gestation or fourfold or greater rise in IgG titer in paired samples.

Parameters	
Paediatric patients	40
Age	
Mean ± SD	4.9 ± 1.1
Median (IQR)	5 (4, 5.5)
Gender	
Male	35% (14)
Female	65% (26)
Patients with symptoms related to cCMV at birth	30% (12)
Maternal age at delivery (years)	
Mean ± SD	30.4 ± 6.2
Median (IQR)	31(25.5, 35)
Duration of follow-up (years)	
Mean ± SD	5.4 ± 1.1
Median (IQR)	5.3 (4.6, 6)
Gestational age at birth (weeks)	
Mean ± SD	37.1 ± 3.2
Median (IQR)	38 (37, 39)
Prematurity < 37 weeks	22.5% (9)
Birth weight (g)	
Mean ± SD	2696.6 ± 377.9
Median (IQR)	2800 (2187.5, 3210)
Birth weight < 2500 g	42.5% (17)
Type of maternal infection	
Primary infection	65% (26)
Non-primary infection	30% (12)
Unknown	5% (2)
Time of maternal CMV infection (trimester)	
First	20% (8)
Second	30% (12)
Third	20% (8)
Unknown	30% (12)
Antenatal US lesions	2.5% (1)
Pathological neuroimaging at onset	25% (10)
Antiviral therapy	27.5% (11)
Positive viremia at onset	75% (30)
Viral Load on blood at onset (IU/mL)	
Mean ± SD	$15 \times 10^3 \pm 67.4 \times 10^3$
Median (IQR)	446 (25.5, 1595)
Viral Load on urine at onset (IU/mL)	
Mean ± SD	$15.3 \times 10^6 \pm 56.1 \times 10^6$
Median (IQR)	9.4×10^5 (6.8×10^4, 4.6×10^6)

Table 1. General characteristics of our sample. *SD* standard deviation, *IQR* interquartile interval.

Patients were classified as symptomatic at onset if presenting with one or more of the following: intrauterine growth restriction, hepatomegaly, splenomegaly, petechiae, thrombocytopenia (< 100,000 platelets/mm^3), elevated serum transaminase levels, jaundice with conjugated hyperbilirubinemia, central nervous system (CNS) involvement (as denoted by microcephaly (head circumference < 2 SD below the mean for age and birth weight), seizures, lethargy and/or poor suck, neuroimaging abnormalities consistent with CMV infection detected by cranial ultrasound (US) and/or Magnetic Resonance Imaging and Computed Tomography in past years such as calcifications, neuronal migration disorders, cerebral, and cerebellar volume loss, ventriculomegaly, white matter disease, ophthalmological abnormalities detected by funduscopic examination or SNHL detected by click-evoked auditory brainstem responses (ABR). SNHL was defined as a threshold ≥ 30 dB nHL for pure-tones, confirmed at two consecutive click-evoked ABR, and after exclusion of middle ear disorders. Patients were defined as asymptomatic if free from all signs listed above soon after birth.

Other causes of congenital infection, including toxoplasmosis, rubella, herpes simplex, and syphilis, were ruled out.

Neonates with CNS involvement were treated with oral valganciclovir for 6 months[23]. If oral route was not available for administration, they were treated with ganciclovir[24]. Parents/legal guardians agreed to treat children and accordingly gave informed consent.

The follow-up was scheduled for 6 years in cases of asymptomatic infection and longer for symptomatic cases, based on clinical needs. Data regarding timing and type (primary vs. non-primary) of maternal infection, neonatal and follow-up evaluations (physical, neurodevelopmental, audiological, and ophthalmological assessments) were prospectively collected during periodic controls. By 3 years of age, we performed a specific vestibular evaluation (see *vestibular assessment*). Data were recorded on a standardized database.

The study protocol matched the standard care applied in our center for all infants with cCMV infection.

Hearing assessment

We adopted different audiological protocols to evaluate the children according to their age.

The objective instrumental evaluation was used for infants ≤ 4 years of age and subjective instrumental evaluation was used in children > 4 years of age. Therefore, transient evoked otoacoustic emissions (TEOAE), click-evoked auditory brainstem responses (ABR) and tympanometry registration were performed on babies ≤ 4 years of age, and, behavioral audiometry or pure-tone audiometry, and tympanometry were performed on children between 5 and 8 years of age. All cCMV patients were subjected to the Universal Newborn Hearing Screening by means of TEOAE and Automated ABR. Based on the results of click-evoked ABR, children were enrolled in a longitudinal audiological follow-up protocol, with scheduled appointments every 6 months until the age of 3 and every 12 months until the age of six.

TEOAEs were performed during spontaneous sleep in a soundproof and faradized room with an automated tool (AccuscreenR Madsen by Natus, Montegrotto Terme, Italy) whose output simply indicates the response score of "pass" or "fail" at 70–80 dB SPL with a frequency range of 1.5–4.5 kHz. TEOAEs will most often be absent when hearing loss is greater than 35 dB HL. In addition TEOAEs may or may not be present when all pure-tone thresholds are between 25 and 35 dB HL, which may lead to missing some hearing-impaired newborns.

Furthermore, the click-evoked ABR (Neuro-Audio by Inventis, Padova, Italy) required spontaneous sleeping in a soundproof and faradized room and detected the presence and the persistence of V wave in order to find the hearing threshold for each side. Normal hearing was defined based on the presence and persistence of V wave for acoustic stimuli < 30 dB nHL. The diagnosis of HL was defined as the presence and persistence of V wave for acoustic stimuli ≥ 30 dB nHL. By using this method, mild SNHL may be missed.

The tympanometry (R36M by Resonance®, Gazzaniga, Italy) measured the middle ear pressure in order to exclude a middle ear dysfunction, suspected in case of a reduced or no measurable middle ear pressure with normal ear canal volume.

Various audiometric procedures as visually reinforced audiometry, conditioned play audiometry and conventional audiometry (R37A, Resonance®, Gazzaniga, Italy) were adopted to identify the pure-tone threshold using frequencies from 0.125 to 8 kHz.

The categorization of HL degree is based on the Bureau International for Audiophonology (Biap) classification[25] and includes: normal (< 20 dB HL), mild (21–40 dB HL), moderate (41–70 dB HL), severe (71–90 dB HL) and profound (> 91 dB HL).

Vestibular assessment

The assessment of vestibular function was performed in children from 3 years of age when they achieve an adequate attention span. This evaluation included a bedside examination, video head impulse test (vHIT) and cervical vestibular evoked myogenic potentials (cVEMPs).

During bedside-examination, eye movements were analyzed with video-oculoscopy (Audiomedical, Pompei, Italy), with and without visual fixation. The assessment included the detection of spontaneous and/or positional nystagmus and head impulse test in order to suspect a vestibular loss.

The vHIT with remote video camera (Synapsys vHIT Ulmer Device, Inventis, Padova, Italy) quantified the vestibulo-ocular reflex and superior vestibular nerve function measuring the ratio (gain) between the eye and head velocities at peak of head acceleration during high-frequency head stimuli/jerk horizontal rotations. The recording of vHIT required at least 5 trials for side and we increased them if the compliance of the patient was high. We used the rejection algorithm of the instrument for those trials where the eye tracking cannot be continued for the whole head movement (for ex. blinking, reduced sharpness) or for insufficient head velocity. Lateral canal hypofunction was defined as a gain value lower than 0.8[26].

The cVEMPs for air conducted sounds (Neuro-Audio, Inventis, Padova, Italy) were performed to evaluate the vestibulocollic reflex and the inferior vestibular nerve function. Potentials were recorded delivering tone bursts of 500 Hz at 100 dB nHL. Recording system used an EMG-based biofeedback monitoring method to minimize variations in muscles contractions and VEMPs amplitudes. A re-test was performed for each stimulus to assess reproducibility and to declare the presence of the biphasic responses. We considered a real vestibular insufficiency the absence of cVEMPs response on at least three consecutive trials[27].

A VD was defined as an abnormal result on at least one test of the vestibular evaluation protocol: selective when only LSCC or otolithic receptors dysfunction occurred, combined in both LSCC and otolithic receptors dysfunction.

Other possible causes of vestibular dysfunction, such as trauma or infections, were excluded based on an accurate anamnesis. Moreover, infected children underwent periodical blood examinations including complete blood count, in the same day of the vestibular assessment, and no pathological findings were highlighted.

Sample size

The sample size was defined using the sample size for proportion. The formula is shown below,

$$N = \frac{z^2_{\frac{\alpha}{2}}\,\pi\,(1-\pi)}{\varepsilon^2}$$

where π is the hypothesized prevalence of successes in the population and ε is the error accepted in the evaluation the sample size. This formula, based on Binomial distribution is applicable whether the distribution is normal or approximately normally. In our study we considered π equal to 60%. Particularly, π was hypothesized as central value of the prevalence interval defined considering the minimum (24.6%) and the maximum (95.7%) prevalence rates reported in review paper by Salomè et al.[28]. Based on $\pi = 60\%$, an error $\varepsilon = 20\%$ and a z-score of 99%, the estimated minimum simple size is equal to 40 children. Our sample was obtained using Bernoulli sampling where all elements of the population had the same probability of being included in the sample. By Bernoulli sampling the sample of 40 children was composed by 12 children with symptoms related to CMV and 28 children without symptoms related to CMV). In our sample the proportion of children with symptoms related to CMV was of 30%, and despite being less than the hypothesized population prevalence (60%), it was included in the estimated prevalence range previous described, and therefore, it was acceptable. Finally, the Binomial distribution of the proportion of 30% can be approximated to normal distribution if the sample size is sufficiently large. Qualitatively, it is possible to consider a sample size as large sample if $N \geq 30$ and $Np > 5$, $N(1-p) > 5$. In our case all the conditions were verified ($N = 40$, $Np = 12$, $N(1-p) = 28$, therefore the previous formula was applicable,

Ethics statement

The study was conducted in accordance with Helsinki Declaration as revised in 2013. The protocol was approved by the Ethics Committee of the University of Naples Federico II (protocol number 274/16 of 2016). Parents/legal guardians of participants provided their written informed consent to participate in this study.

Statistical analysis

Data were presented as number and percentage for categorical variables and continuous data were expressed as the mean ± standard deviation (SD) or median with interquartile interval (IQR). In this study, our sample was stratified into two pairs of complementary and independent subgroups that we compared (Group I: patients without symptoms related to CMV vs. Group II: patients with symptoms related to CMV; and Group III: patients without Vestibular Dysfunction vs. patients with Vestibular Dysfunction). Chi-square test and Fisher's exact test were performed to evaluate significant differences in proportions or percentages between two independent groups. The multiple comparison chi-square and Fisher's exact test were used to define significant differences between two independent groups where the variables were characterized by three or more modalities. If the chi-square or Fisher's exact test were significant (p value < 0.05), the post hoc test was performed using the Adjusted Standardized Residuals and the Z-test, to identify significant modalities with higher and lower frequency. Fisher's exact test was used where the chi-square test was not appropriate, i.e., if the sample size is small ($n \leq 25$), and at least one cell has an expected frequency less than 5. The test for normal distribution was performed using the Shapiro–Wilk test. The t-test was used to evaluate the differences between means of the two independent groups. Alternatively, the Mann–Whitney test was used if the distributions were not normal. Notably, we reported Mean ± SD if the data were normally distributed, while median with IQR if the data were not normally distributed. Furthermore, where the tests on medians showed a significant difference and the medians were equal, then the mean rank values were described. In addition, in the tables with inferential analysis (Tables 2 and 3). the statistical tests used for each comparison were reported. Finally, all tests with p value < 0.05 were considered significant. The statistical analysis was performed using the Matrix Laboratory (MATLAB) analytical toolbox version 2008 (MathWorks, Natick, MA, USA) for Windows at 32 bits.

Parameters	Group I: patients without symptoms related to CMV	Group II: patients with symptoms related to CMV	*p* value (test)
Patients	70% (28)	30% (12)	–
Age			
Median (IQR)	5 (4, 5)	5 (4, 6)	
Mean rank	20.3	21.1	0.83 (MW)
Gender	F: 64.3% (18),	F: 66.7% (8)	1.0 (Fet)
	M: 35.7% (10)	M: 33.3% (4)	
Hearing loss	0% (0)	50% (6)	0.0002* (Fet)
Psychomotor delay	0% (0)	25% (3)	0.024* (Fet)
Vestibular dysfunction	17.9% (5)	66.7% (8)	0.0075* (Fet)
Head Impulse Test (altered)	0% (0)	8.3% (1)	0.36 (Fet)
vHIT—gain < 0.8	17.9% (5)	58.3% (7)	0.021* (Fet)
cVEMPs—absence (n = 38)	3.7% (1)	54.5% (7)	0.0009* (Fet)

Table 2. Comparison between children with and without symptoms related to CMV considering audiological and non-audiological parameters investigated in this study. *p p* value, *C* chi square test, *MW* Mann–Whitney test, *T* t-test, *Fet* Fisher' exact test, *F* females, *M* males. *Significant test (p < 0.05).

Parameters	Group III: patients without VD	Group IV: patients with VD	*p* value (test)
Patients	67.5% (27)	32.5% (13)	
Age			
Median (IQR)	5 (4, 5)	5 (4, 6)	
Mean rank	20	21.6	0.66 (MW)
Gender	F: 66.7% (18)	F: 61.5% (8)	0.28 (C)
	M: 33.3% (9)	M: 38.5% (5)	
Head impulse test	0% (0)	7.7% (1)	0.33 (Fet)
vHIT—gain < 0.8	0% (0)	92.3% (12)	< 0.0001* (Fet)
Hearing loss	0% (0)	46.2% (6)	0.0004* (Fet)
Psychomotor delay	3.7% (1)	15.4% (2)	0.24 (Fet)
Patients with symptoms related to cCMV at birth	14.8% (4)	61.5% (8)	0.0075* (Fet)
cVEMPs—absence (n = 38)	0% (0)	61.5% (8)	< 0.0001* (Fet)
Maternal age at delivery (years)			
Mean ± SD	30.7 ± 6.7	29.9 ± 5.3	0.73 (T)
Duration of follow-up (years)			
Median (IQR)	5.2(4.6, 5.5)	5.9(4.6, 6.7)	0.25 (MW)
Gestational age at birth (weeks)			
Median (IQR)	38.0 (37.0, 39.0)	38.0 (35.75, 38.25)	
Mean rank	21.4	18.5	0.45 (MW)
Prematurity < 37 weeks	18.5% (5)	30.8% (4)	0.44 (Fet)
Birth weight (g)			
Mean ± SD	2820.9 ± 657.8	2438.5 ± 851.5	0.13 (T)
Birth weight < 2500 g % (N)	33.3% (9)	61.5% (8)	0.091 (C)
Type of maternal infection			1.0 (Fet)
Primary infection	63(17)	69.2% (9)	The modality "unknown" was excluded from the analysis
Non-primary infection	29.6% (8)	30.8% (4)	
Unknown	7.4% (2)	0% (0)	
Time of maternal CMV infection (trimester)			0.026* (MFet)
First	11.1% (3)	38.5% (5)**	"First" (Group IV)**, $p = 0.0296$ (Z)
Second	29.6% (8)	30.8% (4)	"Third" (Group III)**, $p = 0.0213$ (Z)
Third	29.6% (8)**	0% (0)	
Unknown	29.6% (8)	30.8% (4)	The modality "unknown" was excluded from the analysis
Antenatal US lesions (yes)	0% (0)	7.7% (1)	0.33 (Fet)
Pathological neuroimaging at onset (yes)	7.4% (2)	61.5% (8)	0.0006* (Fet)
Antiviral therapy	11.1% (3)	61.5% (8)	0.0017* (Fet)
Positive viremia at onset (yes)	63% (17)	100% (13)	0.018* (Fet)
Viral Load on blood at onset (IU/mL)			
Median (IQR)	347 (0, 1710)	918 (252, 4952.75)	0.083 (MW)
Viral Load on urine at onset (IU/mL)			
Median (IQR)	9.2×10^5 (3.1×10^4, 3.7×10^6)	1.3×10^6 (2.1×10^5, 49.6×10^5)	0.31 (MW)

Table 3. Comparison between patients with and without VD considering all audiological and non-audiological parameters investigated in this study. *p p* value, *C* chi square test, *MW* Mann–Whitney test, *T* t-test, *Fet* Fisher' exact test, *F* females, *M* males, *MFet* multiple Fisher' exact test. *Significant test ($p < 0.05$).

Results

Participant characteristics

A cohort consisting of 40 congenitally infected children was examined, with 35% being males (14) and 65% females (26). Enrolled children were all those followed in our clinic who could be evaluated according to inclusion criteria. Age at first vestibular assessment ranged from 3 to 8 years old (mean ± SD: 4.9 ± 1.1). All patients received their diagnosis during the neonatal period, with none diagnosed retrospectively through dried blood spots; 30% (12) were symptomatic at birth. The average follow-up was 5.3 years (range 4.6–6.0). Table 1 shows the information obtained on overall sample.

The auditory function was within the normal range at the first evaluation in all patients with asymptomatic onset and remained stable during the follow-up while 6 (50%) symptomatic children received a diagnosis of SNHL at the onset. The hearing impairment was unilateral in 5 patients and bilateral in 1 patient and all showed also a VD. The degree of unilateral hearing loss in the poorer hearing ear ranged from mild to profound, and it was profound in bilateral hearing loss. Particularly, all children with SNHL and their families received counseling

about hearing loss and its consequences. Three of children with SNHL (2 unilateral and 1 bilateral) received hearing rehabilitation with hearing aids.

Indeed, the VD was highlighted in 13 patients in the overall sample and was associated to hearing loss in 6 children while 7 cases showed only the vestibular loss without hearing impairment even if the bedside examination excluded spontaneous and positional nystagmus in overall sample and detected a positive head impulse test only in a child. Therefore, the instrumental evaluation highlighted the vestibular loss. Among 6 children with VD associated to hearing loss, the detection of vestibular hypofunction was on the same side in 4 (66.6%) patients: 3 cases with unilateral hearing loss and 1 case with bilateral hearing loss. Moreover, VD was combined in both 2 unilateral hearing loss and 1 bilateral hearing loss and selective otolith hypofunction in 1 unilateral hearing loss. Among 7 children with only VD it was combined in 2 patients (alteration of both vHIT and cVEMPs) and selective in 5 patients with the only alteration of vHIT. Regarding the results of the vestibular instrumental evaluation, vHIT detected a reduced gain of the lateral semicircular canal in 12 patients (30.0%). The affected canal was the right side in three cases, the left side in four cases and bilaterally in five cases. The analysis of cVEMPs was performed on 38 out of forty patients showing the absence of the biphasic responses in eight patients: one on the right side, three on the left side and four bilaterally.

Furthermore, 2 patients with unilateral hearing loss showed a bilateral vestibular involvement, one combined and one selective (right reduction of gain at vHIT and left absence of cVEMPs).

In Table 2, we reported the comparison between patients with and without symptoms related to CMV about audiological and non-audiological parameters investigated.

The prevalence of hearing loss (50% vs. 0.0%, $p = 0.0002$), psychomotor delay (25% vs. 0.0%, $p = 0.024$) and VD (66.7% vs. 17.9%, $p = 0.0075$) was significantly higher in symptomatic children. Furthermore, the vestibular instrumental evaluation was significantly more altered in the symptomatic group. In detail, a decreased gain of the LSCC at vHIT was identified in 58.3% of symptomatic patients and in 17.9% of asymptomatic patients ($p = 0.021$), while the absence of cVEMPs was observed in 54.5% of symptomatic patients and in 3.7% of asymptomatic patients ($p = 0.0009$).

Finally, no significant differences between Group I and II were observed for age (mean rank: 20.3 vs. 21.1, $p = 0.83$), and gender (Male: 35.7% vs. 33.3%, $p = 1.0$).

In Table 3 we reported our sample stratified into two groups: children without and with VD. Specifically, in the last column, we compared audiological and non-audiological parameters investigated in this study between the two groups.

Evaluating the pediatrics parameters between children without VD (Group III) and children with VD (Group IV), no statistical difference were observed for maternal age at birth (mean: 30.7 vs. 29.9, $p = 0.73$), for gestational age at birth, considered as weeks of gestation and prematurity, defined as gestational age < 37 weeks of gestation or not (mean rank: 21.4 vs. 18.5, $p = 0.45$), and for birth weight (mean: 2820.9 vs. 2438.5, $p = 0.13$). Both weight measurements were considered as weight expressed in grams and low birth weight, defined as < 2500 g. Furthermore, the duration of follow up did not differ between the two groups (median: 5.2 vs. 5.9, $p = 0.25$).

About time of maternal CMV infection, we found a significant difference between children with and without VD ($p = 0.026$). Namely, the first trimester was associated to children with VD (38.5%, $p = 0.0296$), while the third trimester to children without VD (29.6%, $p = 0.0213$).

Children with VD compared to those without VD presented more frequently neuroimaging abnormalities at onset (61.5% vs. 7.4%, $p = 0.0006$), detected with US and MRI. These abnormalities include multiple calcifications in 5 patients, white matter abnormalities in 2 patients, and a combination of multiple calcifications, white matter abnormalities and micropolygira in one patient with VD, as well as multiple calcifications with subependymal cysts in the 2 patients without VD. They also received antiviral treatment more often (61.5% vs. 11.1%, $p = 0.0017$). In addition, their viremia at the onset was more frequently positive (100% vs. 63%, $p = 0.018$), although a difference in median values of viral load was not highlighted, nor in blood (median: 347 vs. 918, $p = 0.083$) nor in urine (9.2×10^5 vs. 1.3×10^6, $p = 0.31$). Moreover, the presence of antenatal US lesions did not differ in the two groups (0.0% vs. 7.7%, $p = 0.33$).

All the children with symptomatic onset of infection presented cerebral abnormalities at birth, such as germinolytic cysts, cerebral calcifications and ventriculomegaly associated to children with VD compared to children without VD (61.5% vs. 7.4%, $p = 0.0006$), and in 6 cases (46.2%) associated to Hearing loss (46.2% vs. 0.0%, $p = 0.0004$).

For psychomotor delay no significant difference was observed between children with and without VD (15.4% vs. 3.7%, $p = 0.24$).

None of the patients presented neurological signs of VD although one presented with periodic episodes of vertigo followed by vomiting that were initially suspected of cyclic vomiting syndrome and subsequently correctly diagnosed after vestibular evaluation.

Five patients (38.4% = 5/13) were completely asymptomatic both at onset and when vestibular evaluation was performed. In these patients, other causes of VD were ruled out (even with a cerebral MRI).

As described in Table 3, we observed a significant presence of symptoms at birth in children with VD compared to those without VD (61.5% vs. 14.8%, $p = 0.0075$). Furthermore, in the group of children with VD, 46.2% (6/13) had hearing loss., while 53.8% (7/13) had normal hearing function. Therefore, the absence of hearing lossdoesn't assure the proper functioning of the vestibular system.

The VD was more frequently unilateral, 61.5% (8/13) in our cohort.

Children with VD, 53.8% (7/13) had a combined LSCC and otolith dysfunction, 38.5% (5/13) had an isolated LSCC dysfunction, while 7.7% (1/13) had an isolated otolith dysfunction. The vestibular function of the LSCC was affected in 92.3% (12/13) of the vestibular impaired children, while an otolith dysfunction was discovered in 61.5% (8/13). Among the 85% (34/40) of children with normal hearing, 4 children (11.7%) had a canal function

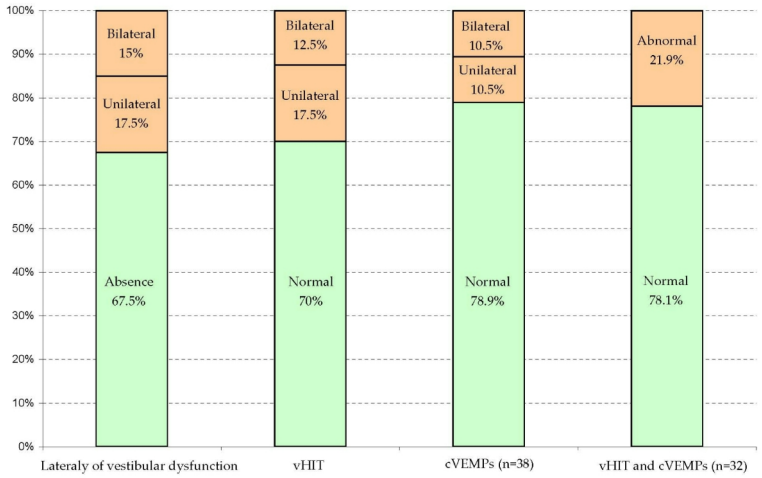

Fig. 1. Vestibular assessment characteristics.

disorder and 8 (23.5%) had otolith damage. More details about semicircular canals and otolith function are showed in Fig. 1.

Discussion

Our study provides findings on the vestibular assessment from a cohort of 40 cCMV-affected patients including 12 infants having symptomatic onset and 6 among them exhibiting SNHL. All children were diagnosed in the neonatal period. In our cohort a compromised vestibular function was found in 13 patients (32.5%), suggesting a higher impact of vestibular damage as compared to the cochlear part of the inner ear.

In most cases, the CMV infection is completely asymptomatic in the child, while in symptomatic patients it is associated with a high rate of comorbidity mainly including neurologic damage as hearing impairment, neurodevelopmental disorders, ophthalmic complications, infantile autism, epilepsy, and other neurologic abnormalities[5].

Several researchers focused on the evaluation of risk factors for the development of SNHL and the implications it can have on neurological development[14,29–32]. Although vestibular disorders in cCMV affected children have been described there are currently few studies on the assessment and features of vestibular damage in these children.

According to a recent review[33] the prevalence of VD ranged from 14 to 90.4% across 12 studies using vestibular-specific assessment. The high variability of the prevalence reported is due to small single center studies, variation in vestibular assessment and limited long-term follow-up of patients.

The lower prevalence of vestibular deficit in our study could be attributed to the enrollment of a greater number of patients with asymptomatic cCMV compared to data reported by Bernard, Dhondt and Maes[14,31,32,34]. In fact, in these studies patients with symptomatic onset and/or severe SNHL represent the majority of analyzed cohorts.

According to the accepted criteria, 8 out of 13 (66.7%) patients with vestibular abnormalities were classified as symptomatic at onset, patients had structural brain abnormalities and 6/8 (75%) had SNHL. Therefore, in our sample the VD in symptomatic children was about four times more reported than in children with asymptomatic onset and with a much higher frequency than reported in literature[35]. Furthermore, in our sample VD (13/40, 32.5%) was more common than SNHL (6/40, 15%) although the occurrence rate of SNHL was slightly higher than the value reported in literature (13%)[7,36].

Due to the anatomic proximity of vestibular organ and cochlea, the association between VD and SNHL is of great interest[19,37], but the mechanism of damage is still poorly understood. The presence of cytomegalic cells with inclusion bodies in the cochlea and vestibular labyrinth, degeneration of the organs of Corti and spiral ganglion cells in the inferior cochlear gyri, and atrophy of the crista and degeneration of nerve fibers in the vestibular system have been demonstrated in human temporal bones. The potassium-regulating structures of the endolymphatic sector of the inner ear, particularly the cochlear stria vascularis and the vestibular dark cells, both primary targets of CMV, are hypothesized to be involved in the etiopathogenesis of hearing loss[38]. The impairment of these structures may result from pressure variations within the inner ear, such as hydrops or atelectasis, which can contribute to the development of hearing loss and vestibular dysfunction[20]. Persistence of the virus in the inner ear has been observed even years after infection, and CMV has been found in the perilymphatic fluid of children who have undergone late cochlear implantation due to progressive hearing loss following cCMV. The reactivation of the virus may produce damage both to the cochlea and to the vestibular system, leading to progressive or late-onset VD, as for cochlear damage[39].

Our functional results demonstrate that the vestibular part of the inner ear is significantly more impaired than the cochlear part confirming the importance of vestibular assessment as part of a neurodevelopmental follow-up in children with cCMV during the first years of life. Furthermore, our data suggest the need of early vestibular evaluations to improve the diagnostic criteria between symptomatic/asymptomatic infants and those

with indication to therapy. Thus, longitudinal vestibular follow-up of all cCMV patients, as established for hearing function, is challenging.

In agreement with the Italian guidelines, in cCMV the surveillance path provides audiological evaluation at 1, 3, and 6 months, then once every 6 months until 3 years of age, and then once a year until age 6[40].

The limitation of our study is that vestibular assessments were performed at a mean age of 4.9 years, hindering the definition of the exact onset time of identified VD. An increasing number of studies have shown that vestibular function loss has a significant impact on motor development and other domains of learning and cognitive abilities, making early identification of vestibular disorders crucial for early rehabilitation[41–44]. However, it is also true that longitudinal vestibular follow-up in all cCMV patients would require a significant commitment from both diagnostic centers and patients. Notably, Dondht et al.[29], in a prospective cohort study including a large cohort cCMV patients with a vestibular assessment before the age of 18 months, identified predictive factors for cCMV-patients at risk for vestibular dysfunction, which have significant effects on motor outcome and hearing impairment at the time of vestibular testing, including the presence of periventricular cysts on the CNS imaging. These findings provide evidence for a targeted vestibular follow-up in cCMV patients with risk factor for VD, mainly hearing impairment and periventricular cysts.

In our study vestibular assessment included canal and otolith function evaluations using vHIT for the assessment of the LSCC function and cVEMPs for an assessment of the otolith function. In line with the results of both Zagólski and Bernard[12,14], semicircular canals dysfunctions were more prevalent than otolith dysfunctions, however, both the canal and otolith system were affected in more than 50% of cases. The vestibular loss was complete in 17.5% and partial in 15% of our cohort (see Fig. 1). The pathophysiologic correlate of this finding remains to be elucidated. On the other hand, the actual number of semicircular canals deficits related to otolith dysfunction might still be underestimated because the cVEMPs test was performed more often successfully than vHIT and rotatory testing[45].

Taken together, cVEMPs responses were absent in 8 cCMV children, frequently monolaterally and in children with hearing loss, indicating a possible CMV role in defective saccular responses. Altered vHIT responses were observed in 12 cCMV children, more frequently bilaterally and in children with normal hearing.

Overall finding on vestibular deficits even in asymptomatic patients with normal hearing function suggests that despite the anatomical and phylogenetic proximity of cochlea and vestibular part the two systems maintain their independent function. Thus, it is important to detect any alteration considering that the initiation of early neuromotor rehabilitation could improve the postural and motor outcomes of children with affected vestibular system[46,47].

In our sample VD is not associated with delayed gross motor development, hypotonia, poor balance and impaired spatial awareness also if these disorders are often not easily reported by patients especially if children. The lack of sufficient linguistic competence to express information about spatial orientation and balance in young children contributes to their symptoms often underestimated. Currently the clinical relevance and practical implications of this condition on balance are not clear. VD does not always lead to balance impairment as children can compensate through vision and proprioception. Moreover, this result could be likely related to the higher prevalence of unilateral VD in our sample. In literature, children with bilateral VD are known to have difficulties with balance[43,47] acquisition of gross motor milestones[21,48,49] and negative impact on cognition, and school performance[42,50–55]. However, the possible impact of unilateral VD on these developmental domains remains unclear. Interestingly, the vestibular test battery adopted in our study provided robust evidence for its feasibility in older children (i.e. over 4 years of age) with VD. Despite, vestibular assessment in children with cCMV as well as in other conditions that could be associated to severe hearing loss or meningitis or in infants underwent to cochlear implantation is highly recommended there is a crucial need to implement vestibular testing in all vestibular-impaired children including below 3 years and even younger 1 year.

The cVEMPs assesses otolith function, while vHIT evaluates the high-frequency function of the semicircular canals, aligning more closely with the physiological stimuli encountered in daily life. This stands in contrast to the caloric test, which appraises mid-frequency and low-frequency function of the LSCC. Given the potential challenges of conducting the caloric test in younger patients, it should be reserved for cases where symptoms are not explained by vHIT or cVEMPs results. Considering that vestibular pathways mature through childhood long-term follow-up from an early age is also crucial to evaluate the reliability of testing and the onset and progression of VD.

Our findings also confirm that there were no differences in vestibular defects in babies born after a maternal primary or non-primary maternal infection, suggesting that both primary or non-primary infection can be equally harmful for the children[32]. In addition, VD was more frequent in case of maternal infection in the first trimester of gestation[32]. In our cohort, the role of maternal antiviral therapy on vestibular function of their children was not evaluable because none of the mothers of children enrolled were treated since treatment was available in Italian clinical practice by December 2020[56]. Further studies will be needed to evaluate the effect of maternal antiviral treatment on vestibular function.

Remarkably, there was no difference in gestational age nor in weight at birth so that these parameters cannot be used as predictors for subsequent development of VD.

However, children with VD presented more frequently neuroimaging abnormalities and received antiviral treatment but these results are consistent with more frequent dysfunction in symptomatic children at birth. Abnormalities on CNS imaging, defined as the presence of periventricular cysts, was found to be a significant predictor for vestibular dysfunction even in another cohort[29]. In our study children with vestibular disfunction presented with more severe features, because abnormalities were mainly calcifications but even white matter abnormalities and micropolygiria. In addition, in our cohort viremia at the onset was more frequently positive in patients with VD although a difference in median values of viral load was not highlighted nor in blood nor in

urine. Our study is the first one that evaluate the predictive role of viral load in blood and urine for VD. Further studies with a large cohort of patients are needed to define this relationship.

Despite the clinical symptoms and functional impairment caused by VD in cCMV patients, very few children have access to the specialized resources required for vestibular testing. Therefore, it is essential to develop a criteria-based approach to prioritize access to these specialized services.

According to our findings, vestibular assessment should be performed in patients classified as symptomatic at onset, particularly in relation to specific clinical presentation characteristics such as structural brain abnormalities (periventricular cysts, calcifications, white matter abnormalities, and micropolygyria) and sensorineural hearing loss (SNHL). Pediatric variables of the infection, which have already been described in the literature as significant predictors, can be used to further refine the criteria for selecting patients for vestibular evaluation. Our results specifically indicate the necessity for prioritized assessment in patients with infections contracted during the first trimester of pregnancy, regardless of the type of infection (primary or non-primary) and the viremia at onset.

Conclusion

Cochlear and vestibular parts of inner ear could be both damaged by cCMV, however, vestibular function seems to more affected as compared to cochlear function. Therefore, vestibular assessment should be recommended during diagnosis and follow-up of infected children together with hearing function evaluation.

Despite most of the vestibular disorders in our sample are combined, isolated LSCC dysfunctions and otolithic dysfunctions are possible. Therefore, determining a vestibular battery test that evaluates all the components of the vestibular system, while being feasible even at an early stage, is crucial in defining effective and feasible protocol in clinical practice.

Our study confirmed that of maternal infection in the first trimester and neuroimaging abnormalities even associated to antiviral treatment in children can be predictive for vestibular defects. Remarkably, positive viremia at the onset can be considered as a risk factor for VD. Future research will be useful to evaluate the role of maternal antiviral therapy on vestibular function in their babies.

Data availability

The datasets generated and analyzed during the current study are not publicly available due to privacy reasons but are available from the corresponding author on reasonable request.

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Author contributions

R.M. and S.S. designed the study. F.G., G.M. and C.Q. actively collaborated to audiological and vestibular evalu-

ation. N.S. performed the statistical analysis. V.D.V and L.C. supervised the manuscript. F.R. and A.R.F. supervised the whole research.

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Declarations

Competing interests
The authors declare no competing interests.

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