Vestibular Disorders in Children With Congenital Cytomegalovirus Infection

Sophie Bernard, MDa, Sylvette Wiener-Vacher, MD, PhDa,b,c, Thierry Van Den Abbeele, MD, PhDabc, Natacha Teissier, MD, PhDabc

BACKGROUND: Congenital cytomegalovirus (CMV) infection is the leading infectious cause of neurologic disabilities and sensorineural hearing loss in children. Sensorineural hearing loss prevalence in CMV suggests a viral tropism for the inner ear. Vestibular disorders induced by CMV infection are underestimated. This is the largest and most thorough study to assess the incidence of vestibular disorders and their correlation with hearing thresholds in children with CMV.

METHODS: This retrospective study assessed a cohort of 52 children with congenital CMV infection and sensorineural impairment who received a complete hearing and vestibular assessment. Vestibular evaluation included clinical examination, caloric bithermal test, earth vertical axis rotation, off-vertical axis rotation, and vestibular evoked myogenic potential. The prevalence, progression, and clinical impact of vestibular disorders were studied and correlated with hearing thresholds and the severity of congenital CMV infection.

RESULTS: Forty-eight children (92.3%) had hearing loss and vestibular disorders. Of those, vestibular disorders were complete and bilateral in 33.3%, partial and bilateral in 43.7%, and partial and unilateral in 22.9%. Serial testing in 14 children showed stable vestibular function in 50% and deterioration in 50%. Congenital CMV infection has a negative impact on postural development that is correlated with neurologic and vestibular impairment. Vestibular disorders were significantly associated with hearing disorders, but their respective severities showed no concordance.

CONCLUSIONS: Vestibular disorders are frequent and severe in CMV-infected children. Routine screening and appropriate management of vestibular lesions is essential to initiate adapted care.

WHAT'S KNOWN ON THIS SUBJECT: Congenital cytomegalovirus infection is the leading infectious cause of neurologic disabilities and sensorineural hearing loss in children. Little is known concerning the frequency and impact of vestibular disorders induced by cytomegalovirus infection.

WHAT THIS STUDY ADDS: This study reports on the largest cohort of vestibular assessment of children congenitally infected with cytomegalovirus, demonstrating vestibular damages, and analyzes the correlations between vestibular dysfunction and hearing impairment or severity of infection. Cytomegalovirus infection affects postural development in children.
Congenital cytomegalovirus (CMV) infection is the leading infectious cause of developmental and neurologic disabilities and sensorineural hearing loss (SNHL) in children. In France, congenital CMV infection currently affects 0.5% of all newborns. Clinical signs in neonates are variable: 5% to 10% are symptomatic at birth, with a mortality rate of up to 10%. Sixty percent may develop cerebral lesions with neurologic sequelae, such as microcephaly, seizures, hypotonia, and feeding disorders, as well as sensorineural sequelae including chorioretinitis and hearing loss. Patients may also have growth retardation, jaundice, organomegaly, and low platelet count. Furthermore, 8% to 15% of asymptomatic neonates will develop neurologic sequelae.

SNHL is the main sequela of this congenital infection, and also the main cause of nonhereditary congenital deafness in humans. Foulon et al performed a prospective study of children with congenital CMV infection and found SNHL in 21% of asymptomatic children and 33% of symptomatic children. They concluded that 22% of all infected children, irrespective of neonatal signs, had some degree of SNHL. A recent review confirmed the incidence of SNHL in 32.8% of symptomatic cases. Other studies showed unilateral SNHL in 33% to 52% of the cases, with all degrees of severity of hearing loss.

The high prevalence of SNHL in children congenitally infected by CMV suggests a viral tropism for the inner ear. Autopsied pediatric CMV cases confirmed that cytomegalic cells were present in the inner ear; lesions were mainly observed in the endolymphatic compartment of the inner ear, particularly in the vestibular structures.

Little research has been carried out on vestibular disorders induced by congenital CMV, and only 2 studies are available. Zagólski suggests that the prevalence of vestibular disorders is probably underestimated and could be higher than that of hearing loss. To date, routine inner ear investigations of these infants include classic audiometric follow-up but not vestibular testing despite strong evidence of vestibular infection.

Methods

Subjects

A retrospective study was carried out in the otorhinolaryngology department of Robert Debré University Hospital from 2000 to 2013. All included patients were diagnosed with congenital CMV infection and underwent vestibular function evaluation. Data concerning hearing and CMV status was also collected (institutional review board approval 951008).

Some patients had several vestibular assessments during their follow-up.
estimate changes in vestibular impairment over time and before cochlear implantation, which itself can lead to vestibular impairment independently of CMV.25

Data Concerning Congenital CMV Infection

Diagnostic Confirmation

All 52 children had a positive urine or saliva culture in the first 2 weeks after birth, positive dried blood spot, or neonatal immunoglobulin M-positive serology.

Clinical and Radiologic Symptoms

Neonatal symptoms of CMV intrauterine infection and the date of vestibular testing were noted. Moreover, cerebral and inner ear abnormalities were investigated by using MRI and computed tomography scans of the brain and temporal bone.

Hearing Evaluation

Hearing assessment was performed in all patients. Transient evoked otoacoustic emissions (TEOAEs) were recorded; if appropriate responses were absent, hearing evaluation was completed with an auditory brainstem response and/or behavioral audiometry tests. Some children underwent several hearing tests. Hearing thresholds were categorized as follows: normal, <20 dB; mild SNHL, 21 to 40 dB; moderate SNHL, 41 to 70 dB; severe SNHL, 71 to 90 dB; and profound SNHL, >90 dB.

Clinical Evaluation of Postural Development and Behavior

The ages of posturomotor control milestone acquisition (head holding, sitting without support, standing with support, and independent walking) were carefully recorded for each child from pediatric medical records (systematically recorded by pediatricians). Data were compared with an age-matched non–CMV-infected pediatric population (n = 58) (data previously published23–28 and determined from our database).

Vestibular and Neurologic Evaluation

Vestibular evaluation included several tests investigating canal and otolith function (Supplemental Information). Our protocol included complete vestibular and neurologic clinical evaluations (including cerebellar, sensitivity, and muscular testing) followed by instrumental testing of vestibular function. Canal function was evaluated at various frequencies with (1) bithermic caloric test (33°C and 44°C) for low frequencies, (2) earth vertical axis rotation (EVAR) with 40°/s2 acceleration and deceleration along a vertical axis for medium frequencies, and (3) head impulse test (HIT) to test the 6 semicircular canals at high frequencies.25 Otolithic function was assessed by using 2 techniques: (1) off-vertical axis rotation (OVAR) with 60°/s constant rotation velocity and 13° axis rotation tilt and (2) cervical vestibular evoked myogenic potential (c-VEMP) with short tone bursts (750 Hz, 4.1/s and 6-ms duration) delivered by air and bone conduction with a control of the electromyogram level for each stimulation.31 The c-VEMP test was performed by using modified brainstem evoked response audiometry equipment (Centor C+, Deltamed, France). The EVAR-OVAR tests were performed using a computer-driven rotatory chair (SAMO, La Roche sur Foron, France), and the vestibulo-ocular responses (VORs) were recorded by electrystagmography more adapted to young children than video recordings.

For the bicaloric tests, the Jongkees formula was applied, in which normal values for relative valence and directional preponderance for children are ±15%. The bicaloric test responses could be normal, absent bilateral, partial symmetric (bilateral symmetric hyporeflexia), or partial asymmetric (one side being or areflexic or hyporeflexic compared with the other side). The HIT test was either normal (no catch-up saccade) or abnormal (presence of a catch-up saccade) for all 6 canals if complete deficit or for some canals in case of partial deficit.

For the c-VEMP, we studied the latencies (ms), thresholds (dB), and amplitude (µV) at 100 dB of P and N waves. The VEMP results could be normal (presence of bilateral P and N with a symmetric amplitude at 100 dB), absent bilateral (absence of P and N), partial symmetric (positive responses only at thresholds >100 dB), or partial asymmetric (difference of thresholds >10 dB and of PN amplitude exceeding 100 µV between the 2 ears).

For the EVAR test, we measured the time constant and maximal initial slow phase velocity of the VOR. For OVAR (otolith stimulation), the parameters analyzed were the bias and the modulation amplitude of horizontal and vertical components of the VOR.27,30

Normal values of EVAR and OVAR were established from a group of 58 age-matched control children with normal clinical vestibular function. The EVAR and OVAR responses could be normal, absent bilateral, partial symmetric (positive response but decreased for the age), or partial asymmetric (significant asymmetry

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<th>Hearing Threshold, dB</th>
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<td>&lt;20</td>
<td>18</td>
<td>17.3</td>
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<tr>
<td>21 to 40</td>
<td>5</td>
<td>4.8</td>
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<tr>
<td>41 to 70</td>
<td>13</td>
<td>12.5</td>
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<tr>
<td>71 to 90</td>
<td>14</td>
<td>13.5</td>
</tr>
<tr>
<td>91 to 119</td>
<td>48</td>
<td>46.1</td>
</tr>
<tr>
<td>&gt;120</td>
<td>6</td>
<td>5.8</td>
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</table>
between the 2 sides or only unilateral response).

For a global vestibular evaluation, we collected all results and defined 8 categories of modifications (Fig 1): areflexia when no response was observed with HIT, caloric, EVAR, and c-VEMP tests; partial and bilateral canal or otolith disorders; partial and unilateral canal or otolith disorders; and normal vestibular function.

**Statistics**

Descriptive statistics and statistical analyses were performed with Epi-info 7 and Excel software. Data are shown as mean (SD). Student t test was used for comparisons between groups. Fisher test was used to assess any correlation between the parameters analyzed for correlation. A P value <.05 was considered statistically significant.

**RESULTS**

**Population Characteristics**

Fifty-two children with congenital CMV infection, 31 females and 21 males, were included in this study and tested for vestibular function. Age at first vestibular examination was 34.7 (28.5) months (range 5 months to 11 years) (Table 1). Fourteen children performed >1 complete vestibular assessment (with a maximum of 7 tests). The average follow-up was 26.3 (23) months (range 1 to 64 months).

**Congenital CMV Infection**

**Clinical and Radiologic Symptoms**

At birth, 22 infants (42.3%) presented with clinical symptoms related to intrauterine CMV infection. These neonatal symptoms included hearing loss (14/22), intrauterine growth retardation (7/22), organomegaly (6/22), thrombocytopenia (8/22), hepatitis (3/22), neurologic disorders (6/22), and hypotonia (3/22).

Neurologic sequelae affected 9 children: 5 with hemiparesis (2 of whom also had seizures), 1 with pyramidal syndrome, 1 with encephalopathy, 1 with fine movement disorder, and 1 with peripheral facial palsy. Nine children had visual disorders.

Cerebral and inner-ear computed tomography and MRI scans showed intracerebral calcifications (8/52), hyperintense signals in the white matter (19/52), ventricular dilations (3/52), and ischemic lesions (1/52).

**Hearing Evaluation**

Hearing loss was diagnosed in 48 of 52 children (92.3%) (4 children had normal hearing). At birth, 26.9% of children (14/52) had hearing impairment, but only 55.8% (29/52) underwent neonatal hearing screening.

Hearing thresholds are presented and classified in Table 2. All degrees of SNHL were observed. Hearing loss was bilateral in 38 children (27 symmetric and 11 asymmetric) and unilateral in 10 children. There was a majority of profound hearing loss (52%) and bilateral symmetric (56.3%) impairment. The hearing impairment was progressive (37.5%), stable (39.6%), or fluctuating (8.3%); for the others (14.6%), the evolution was unknown.

Forty-five patients underwent multiple hearing tests. Hearing thresholds were stable in 19 cases, progressive in 18 cases, and fluctuating in 4 cases.

**Posturomotor Development**

Congenital CMV infection had a significant impact on all stages of posturomotor development (Table 3).

**Vestibular Function Assessment**

Analysis of the various vestibular tests is described in Table 4. In this study, 90.4% of the children (47/52)
had canal dysfunction, and 86.5% (45/52) had otolithic dysfunction. The severity of the vestibular impairment evaluated by each test is summarized in Figs 2 and 3.

The global vestibular assessment for the 52 patients was abnormal in 92.3% of cases (Table 5). Complete bilateral vestibular loss (absence of responses to all tests) was found in 16 of 52 patients (30.8%), partial bilateral dysfunction in 21 patients (40.4%), and partial unilateral dysfunction in 11 patients (21.1%). Among the 21 patients with partial bilateral disorder, an asymmetry between the 2 vestibules was noted in 12 patients.

Of the 14 patients with serial tests, 7 (50%) had stable vestibular function and 7 (50%) had progressive vestibular deterioration over time.

Correlation Between Hearing Impairment and Vestibular Disorders
A statistically significant association was found between the laterality of vestibular disorders and hearing impairment (P = .03). However, no concordance could be demonstrated in the laterality of these disorders (κ = 0.05) (Table 6).

A statistically significant association was found between the severity of vestibular disorders and hearing impairment (P = .02), but the gravity of these disorders showed no concordance (κ = 0.01) (Table 7).

Correlation Between Severity of Congenital CMV Infection and Vestibular Disorders
There was no significant relationship between the initial severity of congenital CMV infection and the gravity of subsequent vestibular disorders (P = .09) (Table 8).

DISCUSSION
To our knowledge, this study reports on the largest cohort of congenitally infected CMV children (n = 52), demonstrating vestibular damages (canal and otolithic function), with complete detailed case histories. Moreover, the analysis of the correlations between vestibular dysfunction and hearing impairment or severity of congenital CMV infection is unique. Our work also demonstrates the impact of congenital CMV infection on postural development in children.

Characteristics of the Population
At birth, 22 of the 52 children (42.3%) were asymptomatic, 17 were diagnosed neonatally by serology or urinary test, and 5 were diagnosed retrospectively on dried blood spot. However, at time of vestibular testing, 98.1% presented with ≥1 symptom corresponding to a sequela of congenital CMV infection.

All children underwent a complete assessment of hearing and vestibular function. We found a very high prevalence of vestibular impairment (92.3%); however, our population may not reflect the general population of CMV-infected children, because some children are referred to our center for...
manifestation of congenital CMV. These data are consistent with those described in the literature, particularly in a prospective study investigating the incidence of CMV hearing loss over a 10-year period.10 Some published studies have found unilateral deafness, of all degrees of severity, in 33% to 52% of cases.12,35 Progressive deterioration of hearing was observed in 11% to 50% of cases, hearing fluctuations in 16% to 23%, and late-onset deafness in 5% to 50%.10,12,35

In our study, hearing loss was diagnosed at a mean age of 15.4 months (SD 20.4 months) (1 child was 7 years old). This is earlier than the mean age of 22 months reported by Fowler in children symptomatic at birth.56 This difference may be due to better hearing screening in recent years.

**Vestibular Assessment**

In our study, vestibular assessments were performed in the same manner, by the same examiner, for all children. However, patient age at the time of vestibular examination was variable (mean 26 months, range 5 months to 11 years). Responses to the different tests were interpreted according to child age.25 We found that vestibular impairment as well as SNHL due to CMV infection can show progressive aggravation over time (50% of the 14 tested children), and we therefore suggest regular follow-up, since progressive vestibular impairment can be asymptomatic.

Vestibular dysfunctions, which were identified in nearly all patients included in our study, were mostly severe and bilateral and concerned both canal and otolith function. Only 7.7% of children (4/52) had normal vestibular function.

Our results are consistent with those first reported by Zagólski in 200821 and Karltorp et al.22 In Zagólski’s study, 16 of 26 children had no response to caloric testing, 12 had no evoked myogenic potentials, and only 8 had normal auditory brainstem response. However, the battery of tests was incomplete, since canal function was assessed only with caloric tests and not evaluated for middle and high frequencies. In the studies of Zagólski and Karltorp et al, otolith function was assessed only for saccular function using air conduction c-VEMP; responses can be absent in young children in cases of middle ear effusion (frequently found), as well as in cases of otolith impairment.

Our study demonstrates the importance of evaluating canal function at medium and high frequencies: 87.8% of children (43/49) had a dysfunction detected with EVAR and 57.7% (30/52) with HIT. Similarly, bone conduction VEMP allowed evaluation of both saccular and utricular function37 even in cases of middle ear effusion: 78.4% (40/51) had abnormal responses. We defined the severity and laterality of canal and otolith dysfunction precisely and performed a global vestibular function assessment. The vestibular loss was complete and bilateral in 30.8% of cases (16 patients) and partial in 61.5% (32 patients).

As previously published, posturomotor development is highly dependent on vestibular function.23,38 Complete bilateral vestibular loss (CBVL) induces severe delay in posturomotor control acquisition, whereas residual vestibular function or unilateral disorders have almost no impact on posturomotor development in young children.23,38
Correlation Between Hearing Loss and Vestibular Dysfunction

Vestibular impairment had the same characteristics as hearing disorders in terms of severity and laterality ($P < .05$). However, vestibular and hearing impairments were not always concordant with each other: severe deafness could be associated with moderate vestibular deficit, and hearing loss in 1 side may be associated with a contralateral vestibular impairment.

Zagólski reported a statistical correlation between vestibular loss and hearing loss: children without hearing impairment showed statistically less vestibular dysfunction. We could not confirm this result because of our small cohort of children with normal hearing ($n = 4$). In Karltop et al, no correlation between hearing loss and the severity or the laterality of vestibular impairment could be found for the 26 candidates for cochlear implant, since all patients had profound SNHL.

Our results suggest that congenital CMV infections induce lesions of cochlear and vestibular parts of the inner ear. This conclusion is supported by histologic studies that show cytomegalic lesions in the cochlea as well as the vestibule. These lesions seem particularly concentrated in the stria vascularis in the cochlea and the dark cells in the vestibule, inducing inner-ear fluid disorders that could explain progressive or delayed inner-ear dysfunction.

Impact on Posturomotor Development

All children were screened for vestibular impairment: 16 had a complete bilateral vestibular loss that required early physical therapy to overcome posturomotor development difficulties; 32 presented with partial vestibular loss. Physical therapy was prescribed only for those who had associated neurologic impairment (14/32).

Based on our results, CMV infection could induce complete bilateral vestibular loss and therefore delay posturomotor development in young children. However, neurologic impairment can also induce delay in posturomotor development.

In comparison with normal development, CMV-infected children have significant delays at each posturomotor milestone. The average age of walking acquisition in CMV-infected children was 18.4 months, 28 months for children with complete areflexia. As the age of walking acquisition has been strongly correlated with the severity of vestibular dysfunction, it has been shown that the earlier CBVL occurs, the stronger the impact on postural motor development.

Once walking is acquired, children with CBVL might fall frequently. Recent studies have shown that CBVL impact may not be limited to posturomotor delays and could also induce cognitive dysfunctions, resulting in attention deficit disorders; learning, reading and writing difficulties; spatial disorientation; or memory retention disorders. These sequelae may also be the consequence of neurologic and oculomotor disorders in CMV-infected children.

The patients included in the study were assessed at a mean age of 3, long after acquisition of the different posturomotor milestones. Appropriate rehabilitation should ideally be given early, in the first 2 years of life, to favor proper development. Bilateral vestibular deficit affects not only posturomotor milestones but also fine movements and gravity perception. These deficits can be undetected or misdiagnosed for neurologic central sequelae. The object of this study is to underline the importance of severe vestibular lesions in CMV patients and the necessity to diagnose complete bilateral vestibular loss as early as possible to recommend early rehabilitation and reduce developmental impact. Children with CMV often accumulate mild to severe neurologic impairment and vestibular impairment. Compensation of vestibular impairment depends on central nervous plasticity but also on its severity and the age it occurred. Long-term sequelae with learning disabilities have been reported by several authors in children with balance and motor dysfunction.

<table>
<thead>
<tr>
<th>TABLE 7 Correlation Between Severity of Hearing Impairment and Severity of Vestibular Disorders</th>
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<tbody>
<tr>
<td>Severity of Hearing Deficits</td>
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<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Bilateral profound</td>
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<td>Partial</td>
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<td>Normal</td>
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Data are expressed as the number of children. There is a significant relationship between the laterality of the disorders ($P = .023$), but these are not correlated ($\kappa = 0.01$).

<table>
<thead>
<tr>
<th>TABLE 8 Correlation Between the Severity of Congenital CMV Infection and the Severity of Vestibular Disorders</th>
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<tbody>
<tr>
<td>Severity of Vestibular Deficits</td>
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<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Bilateral areflexia</td>
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<tr>
<td>Partial</td>
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<td>Normal</td>
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<td>Total</td>
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There is no significant relationship ($P = .09$).
Vestibular disorders and no neurologic impairment. In our experience, most children with complete congenital bilateral vestibular loss do not catch up with their peers (S. Wiener-Vacher, unpublished data).

Among the 52 children infected with CMV, 21% showed obvious signs of neurologic impairment, but this does not exclude subliminal neurologic disorders that may be revealed later during development. In CMV-infected children with axial hypotonia, delayed walking, and frequent falls, CBVL alone can explain such a clinical pattern, suggesting that neurologic impairment is not severe. In contrast, diagnosing a partial vestibular impairment is not severe. In contrast, a clinical pattern, suggesting that neurologic dysfunction cannot explain such a clinical pattern.

CONCLUSIONS

Vestibular disorders are frequent and severe in children congenitally infected with CMV. Both canal and otolith functions are affected. Considering the impact of complete bilateral vestibular loss on posturomotor development, screening and monitoring for vestibular disorders should be included in standard assessment and follow-up of CMV-infected children. Practitioners must screen for vestibular disorders that are frequent in CMV. This is particularly important in cases of posturomotor development delay that can be due to either neurologic impairment or complete bilateral vestibular loss, both of which require early and adapted physical therapy to avoid long-term consequences. Complete bilateral vestibular loss induces low dynamic visual acuity, loss of gravity perception, and spatial disorientation that can lead in absence of intervention to learning disabilities and perturbed fine motor control (misdiagnosed for dyspraxia).

ABBREVIATIONS

CBVL: complete bilateral vestibular loss
CMV: cytomegalovirus
c-VEMP: cervical vestibular evoked myogenic potential
EVAR: earth vertical axis rotation
HT: head impulse test
HST: head-shaking test
OVAR: off-vertical axis rotation
SNHL: sensorineural hearing loss
TEOAEL: transient evoked otoacoustic emission
UVL: unilateral vestibular loss
VOR: vestibulo-ocular response

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Congenital cytomegalovirus infection. 


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