Vestibular, Gaze, and Balance Disorders in Asymptomatic Congenital Cytomegalovirus Infection
Swetha Pinninti, MD,a Jennifer Christy, PT, PhD,a Anwar Almutairi, PT, PhD,b Graham Cochrane, BA,b Karen B. Fowler, PhD,a,c Suresh Boppana, MDa,d

abstract

BACKGROUND AND OBJECTIVES: Congenital cytomegalovirus (cCMV) is the leading nongenetic cause of sensorineural hearing loss and developmental disabilities. Because there are limited data from studies of vestibular involvement in select groups of children with cCMV, the true frequency of vestibular disorders in cCMV is likely underestimated. Our objective for this study is to determine the prevalence of vestibular, gaze, and balance disorders in a cohort of children with asymptomatic cCMV.

METHODS: Comprehensive vestibular, gaze, and balance assessments were performed in 40 children with asymptomatic cCMV. The function of semicircular canals of the inner ear and vestibulo-visual tract were assessed by measuring vestibulo-ocular reflex in a computer-driven motorized rotary chair; inner ear saccular function was assessed by using cervical vestibular evoked myogenic potential; gaze stability during head movement was assessed by using clinical dynamic visual acuity, and balance was assessed by using the sensory organization test and the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition. Test results for each variable were compared with those of a control group without cCMV and/or compared to age-matched normative published data.

RESULTS: Vestibular disorders were evident in 45% of the cohort on the basis of rotary chair and cervical vestibular evoked myogenic potential testing, suggesting abnormalities in semicircular canals, the utricle and saccule of the inner ear, and vestibulo-visual tracts. Additionally, 46% of the cohort had difficulties maintaining gaze during head movement, and one-third to one-half of the cohort had difficulties maintaining balance.

CONCLUSIONS: Vestibular, gaze, and balance disorders are highly prevalent in children with asymptomatic cCMV. Systematic screening for vestibular disorders will be used to determine the full clinical impact for the development of effective interventions.

WHAT’S KNOWN ON THIS SUBJECT: Hearing loss is the most common sequel in children with congenital cytomegalovirus (cCMV), including those with asymptomatic infection. However, the prevalence and extent of vestibular, gaze, and balance disorders in cCMV, particularly in children with asymptomatic infection, is not well defined.

WHAT THIS STUDY ADDS: We document a high prevalence of vestibular, gaze, and balance disorders in children with asymptomatic cCMV, highlighting the need for routine vestibular testing in all children with cCMV; the need for future studies to determine the clinical impact, and the need for developing clinical interventions.


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DOI: https://doi.org/10.1542/peds.2019-3945
The prevalence of congenital cytomegalovirus (cCMV) infection in the United States is estimated to be 4.5 per 1000 live births.\(^1\)

Sensorineural hearing loss (SNHL) is the most common and well-characterized sequela in children with cCMV, responsible for 8% to 40% of all childhood hearing loss.\(^2\)\(^-\)\(^6\)

Most infants with cCMV do not have clinical abnormalities at birth (asymptomatic), and \(~\)10% to 15% of these children develop SNHL.\(^7\)\(^-\)\(^12\) The natural history of cytomegalovirus (CMV)–associated SNHL is well defined, and audiological monitoring of children with cCMV\(^13\) is recommended because SNHL is of varying severity and could be late onset, fluctuate, or progress over time.\(^14\)\(^-\)\(^16\)

Although SNHL is recognized as the most common sequela of cCMV,\(^2\)\(^,\)\(^7\) despite histopathologic evidence of the presence of CMV in the vestibular organ from studies of fetuses with CMV infection,\(^17\)\(^,\)\(^18\) limited data exist regarding vestibular disorders\(^19\)\(^-\)\(^23\) in children with cCMV. In children with SNHL,\(^24\)\(^-\)\(^27\) or vestibular hypofunction from birth,\(^28\)\(^-\)\(^30\) due to other etiologies, there is abundant evidence for progressive developmental delays, aberrant postural control, and poor gaze stability, leading to difficulties participating in sports, performing high-level gross motor functions, and reading.\(^31\) Additionally, vestibular and balance physical therapy in these children has been shown to improve gross motor, balance, and gaze outcomes.\(^32\)\(^,\)\(^33\) Our objective for this study is to determine the prevalence of vestibular, gaze, and balance disorders in children with asymptomatic cCMV identified by newborn screening.

**METHODS**

**Study Participants**

Between March 2007 and March 2012, newborns at 7 US medical centers were enrolled in the Cytomegalovirus & Hearing Multicenter Screening (CHIMES) Study within the first 3 weeks of life and tested for CMV by using rapid culture or polymerase chain reaction of saliva and/or urine. Of the 100,332 newborns screened, 449 (0.45%) were confirmed to have cCMV and were managed long-term for hearing loss outcomes for 5 years.\(^1\)\(^3\)\(^4\)\(^,\)\(^3\)\(^5\) Initial newborn screening methodologies have been described previously.\(^3\)\(^4\)\(^,\)\(^3\)\(^5\)

Newborns who tested positive for CMV with normal physical examination findings at birth were considered to have asymptomatic cCMV and were managed long-term for hearing loss outcomes. Forty of these children enrolled at The University of Alabama at Birmingham (UAB) site of the CHIMES Study consented to participate in the current study for vestibular, gaze, and balance testing.

The control group constituted 33 healthy children without hearing loss who participated in other research protocols at UAB from whom the control group were matched normative published data.\(^2\)\(^9\)\(^,\)\(^3\)\(^0\)\(^,\)\(^3\)\(^7\) Institutional review board approval was obtained for this study.

**Audiological Assessments**

Children with cCMV underwent audiological assessments per CHIMES protocols\(^3\)\(^8\) and had at least one follow-up hearing assessment in the year before performance of vestibular assessments.

**Tests of Vestibular Function, Gaze, and Balance**

The vestibular system is a complex network and includes (1) the semicircular canals (SCCs); (2) the otolith organ (utricle and saccule); (3) visual, somatosensory, and vestibular pathways to the brain; and (4) the vestibulospinal tracts and is primarily responsible for spatial awareness, stability of the eyes during head movement (gaze stability), and maintenance of balance. The tests used to assess the different components of the vestibular system are briefly described here and summarized in Fig 1.

**SCCs and Vestibulo-Visual Tract**

The integrity of the horizontal SCC and associated brainstem level reflexes is assessed by measuring the vestibulo-ocular reflex (VOR) by using videovestibulography and a computer-driven rotary chair (RC). A precise description of the RC testing protocol is described elsewhere.\(^3\)\(^6\)\(^,\)\(^3\)\(^9\) An overall VOR score was calculated and considered abnormal if sinusoidal harmonic acceleration testing performed at 1.28 Hz was \(<\)1 SD of the data derived from the control group.

The function of the vestibulo-visual tract, mediated by the utricle and the central utricular pathways, is assessed by subjective visual vertical variance (SVV), which measures the participant’s perception of the vertical and horizontal, and also by measuring VOR cancellation.

**Saccule**

Saccular function is measured by cervical vestibular evoked myogenic potential (cVEMP), per published methods.\(^3\)\(^6\)\(^,\)\(^3\)\(^9\) Tymanometry preceded all protocols to ensure integrity of the middle ear. Test results \(<\)1 SD of the normative data derived from the control group were considered as low amplitude or abnormal results. The response result was coded as normal (normal response in both ears), partial and asymmetric (diminished unilaterally), partial and symmetric (diminished in both ears), weak bilaterally, or absent bilaterally.
**Gaze Stability**

Clinical dynamic visual acuity (cDVA) is used to test the integrity of gaze stability and assess the functional use of VOR. Visual acuity completed with the head static and then as the head was passively moved at 2 Hz was measured. The difference between static and dynamic visual acuity of >2 lines was coded as abnormal, suggestive of inability to use the VOR to see clearly during head movement.39

**Statistical Analysis**

The prevalence of vestibular, gaze, and balance abnormalities was determined for the entire group. Medians with ranges were calculated for nonnormal data, and P values were calculated by using Student’s t test. The Mann–Whitney U test was used to calculate the differences in scores for each assessment between the two groups. P values <.05 were considered statistically significant. As outlined in the Methods section, for VOR, SVV, VOR cancellation, cVEMP, and SOT assessments, results <1 SD of the scores for the control group were coded as abnormal for the cCMV group. For cDVA and BOT-2, the data from the cCMV group were compared to age-appropriate published data.39,30

**Results**

Demographic information for the entire cohort is summarized in Table 1. Of note, a majority of children from the cCMV group were Black compared with the controls (68% vs 6%; P < .001), consistent with demographics from the UAB site of the CHIMES Study and with higher prevalence of cCMV among Black infants.1 There were no significant differences between maternal sociodemographic factors between children with cCMV in this study and the rest of the CHIMES cohort. Of the 40 children with cCMV, 17.5% (7 of 40) had SNHL; 6 of 7 (2 children each with mild, moderate-severe, and profound-degree SNHL and one with late-onset SNHL) with unilateral hearing loss and one child with bilateral SNHL. Results of vestibular, gaze, and balance tests for the entire group are summarized in Table 2, and a summary of test results in children with cCMV with SNHL is presented in Table 3.

**RC Testing**

Of the 37 children who underwent RC testing, 29 completed SCC function testing, of whom, 44.8% (13 of 29) were noted to have low VOR overall. None of the children tested had a complete absence of VOR. The median VOR gain for the cCMV group was lower compared with the control group (0.81 [range: 0.40–1.20] vs 1.01 [range 0.70–1.30], respectively; P = .002), as shown in Table 4.

Of the children who completed SVV testing and VOR cancellation, 20% (7 of 35) and 40.5% (15 of 37), respectively, scored outside the normal range. There was no significant difference between median scores for both the groups for these tests (Table 4). Nine of 13 children with an abnormal VOR overall, 6 of 7 with an abnormal SVV, and all the 15 children with an abnormal VOR cancellation result had normal hearing.

**cVEMP**

Of the 38 children who completed cVEMP testing, 44.7% (17 of 38) had a diminished or absent cVEMP response in at least 1 ear (5 with partial asymmetric response, 5 with unilateral absent response, 5 with weak bilateral responses, and 2 with a partial symmetric response). Among children with cCMV with an abnormal cVEMP, 14 of 17 had normal hearing, whereas 3 with SNHL had an
abnormal cVEMP ipsilateral to the side of hearing loss.

**cDVA**

Of the 39 children with cCMV who completed cDVA testing, 48.7% (19 of 39) scored abnormal, including 15 of 19 with normal hearing, suggesting that these children have difficulty maintaining stable vision during head movement.

**SOT**

Thirty-nine children with cCMV completed SOT testing. The somatosensory, vestibular, and visual ratios were found to be abnormal in 23%, 53.8%, and 30.8%, respectively, suggesting difficulties integrating these inputs to maintain balance. The median SOT composite score was significantly lower in the cCMV group compared with the control group (Table 4). Interestingly, 6 of 7 children with SNHL had an abnormal SOT composite score.

**BOT-2**

Sixteen of the 38 (42%) children who completed BOT-2 testing scored below average compared to age-matched published data. Of those tested with an abnormal result, 13 of 16 children had normal hearing.

**DISCUSSION**

The current study highlights the frequent occurrence of vestibular disorders in children with asymptomatic cCMV on the basis of comprehensive vestibular, gaze, and balance testing. Given the anatomic and phylogenetic proximity of cochlear and vestibular organs in the inner ear and recognizing that SNHL is the most common sequela in children with cCMV, we anticipated vestibular disorders would be more prevalent in children with cCMV-associated SNHL. However, the findings of this study document vestibular disorders not only in children with cCMV-associated SNHL but also in children with normal hearing, suggesting vestibular involvement might be independent of hearing status.

In one of the earliest studies of vestibular system assessments in cCMV, Pappas performed vestibular testing using hot and cold caloric tests in 11 children with asymptomatic cCMV. Six (54%) children were noted to have a complete lack of, or hypoactive, vestibular response with delayed gross motor skills. For the current study, we opted out of caloric test because it invokes vertigo and discomfort and only provides

### TABLE 1 Demographic Data

<table>
<thead>
<tr>
<th>Sex, n (%)</th>
<th>cCMV Group (n = 40)</th>
<th>Control (n = 33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>20 (50)</td>
<td>13 (39)</td>
<td>.37</td>
</tr>
<tr>
<td>Male</td>
<td>20 (50)</td>
<td>20 (60.3)</td>
<td>.001</td>
</tr>
<tr>
<td>Race and/or ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>25 (67.5)</td>
<td>2 (6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>12 (25)</td>
<td>20 (60.6)</td>
<td></td>
</tr>
<tr>
<td>White Hispanic</td>
<td>3 (7.5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>8 (24)</td>
<td></td>
</tr>
<tr>
<td>Multiracial</td>
<td>0</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>SNHL, n (%)</td>
<td></td>
<td></td>
<td>.01</td>
</tr>
<tr>
<td>Unilateral</td>
<td>7 (17.5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>1</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Mean age, y ± SD</td>
<td>7.52 ± 1.2</td>
<td>9.7 ± 1.6</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

—, not applicable.  
* Two each with mild, moderate-severe, and profound unilateral SNHL.

### TABLE 2 Summary of Vestibular Assessment Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Testing Completed, n</th>
<th>Abnormal Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total, n (%)</td>
<td>Normal Hearing, n</td>
</tr>
<tr>
<td>SCC function</td>
<td>29</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>VOR (1.28 Hz)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vestibulo-visual tract</td>
<td>35</td>
<td>7 (20)</td>
</tr>
<tr>
<td>SVV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VOR cancellation</td>
<td>37</td>
<td>15 (40.5)</td>
</tr>
<tr>
<td>Saccular function</td>
<td>38</td>
<td>17 (44.7)</td>
</tr>
<tr>
<td>cVEMP</td>
<td>39</td>
<td>19 (48.7)</td>
</tr>
<tr>
<td>Dynamic visual acuity</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>cDVA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tests of balance</td>
<td>59</td>
<td>8 (23)</td>
</tr>
<tr>
<td>Somatosensory (SOT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vestibular (SOT)</td>
<td>59</td>
<td>21 (53.8)</td>
</tr>
<tr>
<td>Visual (SOT)</td>
<td>59</td>
<td>12 (30.8)</td>
</tr>
<tr>
<td>BOT-2</td>
<td>58</td>
<td>16 (42.1)</td>
</tr>
</tbody>
</table>
information regarding horizontal SCC function at low frequencies. Instead, we performed comprehensive vestibular assessments using the RC to test horizontal SCC and utricular functions and cVEMP to test saccular function of the inner ear.

This study is one of the few in which comprehensive vestibular testing is performed by using an RC. Bernard et al.22 documented vestibular disorders and hearing loss in 92.3% of a cohort of children with cCMV in whom RC testing was performed. The lower prevalence of vestibular disorders in our study (44.8% with abnormal VOR overall and 20% with abnormal SVV on RC testing) is likely due to inclusion of children with only asymptomatic cCMV and fewer children with SNHL. Moreover, gaze and balance assessments were not performed in the study by Bernard et al.22 and because their cohort predominantly included children with severe SNHL, the study findings are difficult to generalize. Vestibular disorders in children with and without hearing loss are documented in both studies, highlighting the need for vestibular screening in all children with cCMV.

Notably, 44.7% of children in our cohort who underwent cVEMP testing, including 14 children with normal hearing, had an abnormal response. In 2 previous studies, researchers performed cVEMP testing in asymptomatic infants with cCMV and documented normal cVEMP results (compared to 44.7% of children with abnormal cVEMP results in the current study) likely because of technical difficulties of sustaining the sternocleidomastoid muscle contraction needed for cVEMP testing when performed in younger age groups (testing performed at median ages of 3 and 6 months, respectively, in the previous studies versus 7 years in the current study).20,23

With our study, we are the first to evaluate and report gaze stability and balance disorders in children with asymptomatic cCMV on the basis of definitive testing (cDVA, SOT, and BOT-2), suggesting abnormal integration of sensory input. Previously, Karltop et al.21 documented balance disturbances and motor delay in 88% of children in a cohort of children with symptomatic cCMV who underwent cochlear implantation, whereas Maes et al.23 documented no evidence of motor delays among children with asymptomatic cCMV. The variability in observed results for vestibular and balance testing across studies is likely due to differences in patient populations, severity of cCMV, severity of SNHL, and differences in methodologies used because of lack of evidence-based guidelines, as exist for hearing loss in cCMV.13

A major strength of this study is the inclusion of children with asymptomatic cCMV, identified prospectively by newborn screening, highlighting vestibular, gaze, and balance disorders in cCMV irrespective of severity of infection or hearing status. This is, so far, the largest cohort of children with asymptomatic cCMV assessed for vestibular, gaze, and balance disorders.

The few limitations of this study include the small sample size, the inclusion of a small number of children with SNHL in the cCMV cohort, and difficulties in performing cVEMP because of technical difficulties of sustaining muscle contraction needed for cVEMP testing when performed in younger age groups.

<table>
<thead>
<tr>
<th>TABLE 3 Summary of Results for Children With cCMV and SNHL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subject</strong></td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

L, left ear; NA, not administered; NC, not completed; R, right ear; X, abnormal test result; √, normal test result.

<table>
<thead>
<tr>
<th>TABLE 4 Comparison of Vestibular and Balance Assessment Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vestibular Tests, Median (Range)</strong></td>
</tr>
<tr>
<td>--------------------------------------------------------------</td>
</tr>
<tr>
<td>1.28-Hz VOR</td>
</tr>
<tr>
<td>SVV</td>
</tr>
<tr>
<td>VOR Cancellation</td>
</tr>
<tr>
<td>cVEMP</td>
</tr>
<tr>
<td>cCMV cohort</td>
</tr>
<tr>
<td>cCMV without SNHL</td>
</tr>
<tr>
<td>cCMV and SNHL</td>
</tr>
<tr>
<td>Control group</td>
</tr>
<tr>
<td>P</td>
</tr>
</tbody>
</table>

Parameters presented in this table are assessments that were compared between test and control subjects.

* Represents comparison between cCMV cohort and control group.
group, and the lack of children with SNHL in the control group. Despite
the small sample size, however, we
document high prevalence rates of
vestibular, gaze, and balance
disorders in this cohort, irrespective
of hearing status, and highlight the
need for universal vestibular, gaze,
and balance assessments in
children with cCMV. Another major
limitation is that the full clinical
impact of these
findings on sports
participation, school performance,
and daily activities was not
assessed through parent interviews
and review of school records.
Therefore, the findings of this study
need to be validated in a larger
cohort with clear de
inition of the
clinical impact of these disorders to
assess the need for development of
interventions. It should also be
noted that because the RC only
measures VOR in response to
medium-frequency head
movements and thus only assesses
the function of horizontal SCCs,
future studies should include testing
with the video head impulse test,
which measures VOR in all canals in
response to high-velocity head
movements.40

CONCLUSIONS
In a cohort of children with
asymptomatic cCMV identified by
newborn screening, we document the
frequent occurrence of vestibular,
gaze, and balance disorders.
Development of standardized
vestibular, gaze, and balance testing
protocols is necessary to enable
identification of all affected children
to determine the clinical impact and
develop effective clinical
interventions.

ABBREVIATIONS
BOT-2: Bruininks-Oseretsky Test
of Motor Proficiency, Second Edition

CMM: congenital cytomegalovirus
CDVA: clinical dynamic visual
acuity

CHIMES: Cytomegalovirus &
Hearing Multicenter
Screening

CMV: cytomegalovirus
cVEMP: cervical vestibular evoked
myogenic potential

RC: rotary chair

SCC: semicircular canal

SNHL: sensorineural hearing loss

SOT: sensory organization test

SVV: subjective visual vertical

variance

UAB: The University of Alabama at

Birmingham

VOR: vestibulo-ocular reflex


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