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Diversity of the Cochlear and Vestibular Pathologies in Human Temporal Bones of Newborns infected with Cytomegalovirus

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Abstract

Hypothesis: Human temporal bones of newborns with congenital cytomegalovirus (cCMV) infection can be characterized by diverse cochlear and vestibular histopathologies associated with the variability in sensorineural hearing loss (SNHL) and vestibular dysfunction in these newborns.

Background: Only a small number of studies on the cochlear and vestibular pathologies in human temporal bones with cCMV infection have been previously reported.

Methods: Cochleovestibular histopathologies were evaluated in 4 temporal bones from 3 infants with cCMV infection by light microscopy.

Results: In one available temporal bone of the infant in Case 1, no cytomegalic cells were found. Large areas of cellular and non-cellular structures were observed in the scala tympani of the perilymphatic space; however, there was no obvious loss of cochlear or vestibular hair cells. In Case 2, cytomegalic cells, a loss of vestibular hair cells, and a loss of nerve fibers were observed only in the area of dark cells in the vestibular labyrinth of the left temporal bone. No cytomegalic cells were found in the right temporal bone of the same infant; however, there was a loss of outer hair cells in the organ of Corti and hypervascularity in the stria vascularis. The one available temporal bone of the infant in Case 3 showed cytomegalic cells and a loss of hair cells in both cochlear and vestibular parts of the inner ear.

Conclusions: Human temporal bones of newborns with cCMV demonstrate diverse cochleovestibular histopathologies. This diversity is consistent with the variable SNHL and vestibular dysfunction reported in infected newborns.

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INTRODUCTION

CMV is a DNA virus of the *Herpesviridae* family. Congenital CMV (cCMV) infection is the most common infection in newborns, affecting approximately 30,000 infants in the United States each year [1] and infection causes hearing loss and other neurological disabilities in 15-20% of infected infants [2]. Hearing loss associated with cCMV is sensorineural; it can be of varied severity, unilateral or bilateral, progressive or fluctuating [3,4]. Currently, treatment options for hearing loss are limited to hearing aids for mild and moderate cases and cochlear implants for severe and profound hearing loss. There are data from randomized controlled trials that infants with symptomatic cCMV treated with anti-CMV drugs, ganciclovir and valganciclovir [5,6], demonstrate improved hearing and neurodevelopmental outcomes. There is no effective way to prevent CMV transmission from a CMV-infected mother to a developing fetus, although not all maternal infections result in vertical transmission. Development of CMV vaccines is the most promising strategy for preventing cCMV infection and neurological sequelae, including hearing loss [7].

In addition to SNHL, there is increasing evidence that cCMV infection results in vestibular dysfunction. Rotary chair and cervical vestibular evoked myogenic potential testing showed that vestibular impairment of the inner ear is also frequent [8,9]. It may exist with or without hearing loss and be more severe than the associated hearing loss; conversely, hearing loss may occur without vestibular dysfunction. Similar to hearing loss, vestibular dysfunction in cCMV infection can be highly variable: it may be unilateral or bilateral, limited or extensive, stable or progressive [10].

The mechanism of hearing and vestibular loss caused by cCMV has been studied in experimental animal models and human temporal bones. Postnatal infection studies in mice demonstrated inflammatory cells (macrophages and T-cells) in some cochlear regions also positive for virus [11], the

degeneration of the vascular system in the stria vascularis, and a decrease in spiral ganglion cell density after infection [12,13]. In different tissues with high CMV loads, the presence of virus can be found by observation of cytomegalic cells with characteristic inclusion bodies [14]. Cytomegalic cells in the inner ear were initially reported in human temporal bones of newborns with cCMV [15] and later in guinea pigs, after injection of CMV into the scala tympani of the inner ear [16].

Analyses of temporal bones of newborn infants and fetuses revealed cytomegalic cells in the cochlear duct, the organ of Corti, Reissner's membrane, the stria vascularis, and other locations. There were also numerous cochlear histopathologies: loss of outer and inner hair cells, degeneration of the organ of Corti, loss of the spiral ganglion cells, and abnormalities of the stria vascularis and Reissner's membrane [15,17-23]. In the vestibular system of infants with severe cCMV infection, an accumulation of cytomegalic cells in the areas of dark cells, loss of hair cells in the macula of the utricle, saccule, and semicircular canals, and degeneration of nerve fibers were all observed [19-21,24]. There is only one review on the clinical and histopathologic findings in 9 human temporal bones of newborns with cCMV infection [19]. Because of the limited number of postmortem temporal bone specimens of infants with congenital and postnatal CMV, the histopathological basis of CMV-induced SNHL and vestibular dysfunction is not well understood.

he aim of this study was to determine the diversity of cochlear and vestibular pathologies in human temporal bones of newborn infants with cCMV infection in order to better understand the underlying pathophysiology of SNHL and vestibular disorders. To demonstrate the diversity of CMV-induced histopathologies in human ears, infected temporal bones were analyzed for a new case (Case 1) and two cases (Cases 2 and 3) we have previously reported (23). In contrast to our previous publication [23], in this study, we compared both auditory and vestibular parts of each temporal bone for 4 available temporal bones from 3 newborn patients (Cases 1-3), including left and right temporal bones of the same patient (Case 2).

MATERIALS AND METHODS

Four human temporal bones were removed after death from 3 deceased newborns with cCMV infection from the Otopathology laboratory at the University of Minnesota, Minneapolis, MN (Cases 1) and from Massachusetts Eye and Ear Infirmary, Boston, MA (Cases 2 and 3). Temporal bones from pediatric patients (0-18 years old) without CMV or other ear diseases and with short postmortem times (<6 hours) were used as controls. The Institutional Review Boards of the University of Minnesota approved this study (0206M26181). The article does not include any studies with human participants performed by any of authors.

CASE REPORTS

Case 1

represents cCMV infection with detailed clinical history. This 12-week-old girl born as triplet had extremely low birth weight (650 g). She was intubated for respiratory failure and had several postnatal workups. Renal ultrasonograms found enlarged kidneys and increased echogenicity that prompted an infectious disease workup. Her urine and blood were positive for CMV. CMV PCR test showed about 870,000 IU/ml for whole blood on day 18. She was placed on ganciclovir but disconnected after a 12 day course for neutropenia. She was eventually placed on Do Not Resuscitate/Do Not Intubate (DNR/DNI). The temporal bones were removed (postmortem time - 3 hours); only the right temporal bone was available for histopatological analysis.

Case 2

This 11-day full-term old boy was icteric with an enlarged liver and spleen and generalized petechiae. In spite of a complete blood volume exchange transfusion, the bilirubin count continued to rise to level 5.3 mg/dL. After 6 days, hypothermia and anemia were noted. His clinical condition worsened with elevated liver enzymes, and he succumbed nine hours later. Autopsy findings revealed a widely disseminated CMV infection associated with a necrotizing enterocolitis. Cause of death was diagnosed as hypotensive shock following massive hemolysis secondary to disseminated cCMV infection. Both right and left temporal bones were removed (postmortem time - 10 hours) for histological analysis.

Case 3

This 3-week-old girl became jaundiced and developed hepatomegaly when she was 2 days old. She was immediately admitted to the hospital and received two exchange blood transfusions. She was diagnosed with erythroblastosis fetalis. Two weeks later she developed exfoliative dermatitis, severe dehydration, and died despite intensive treatment. Autopsy revealed cytomegalic cells in the convoluted tubules of the kidney and many other organs. The temporal bones (postmortem time - 14 hours) were removed and the right temporal bone was processed for histological analysis.

All temporal bones were fixed in formalin, decalcified in ethylene tetrameric acid (EDTA) and embedded in celloidin. Serial sectioning was performed in the horizontal plane at a thickness of 20 μm. Every tenth section was stained with hematoxylin and eosin (H&E) and mounted on glass slides for light microscopy. In some cases, to identify the types of vestibular hair cells, differential interference contrast (DIC) microscopy was used.

In spite of autolytic postmortem changes, the loss or damage of the inner ear structures in temporal bones with cCMV infection could be seen compared to control bones of patients with no history and histological signs of ear diseases. We characterized the presence of cytomegalic cells with CMV inclusion bodies, loss of hair cells, and abnormalities of the stria vascularis in the cochlea. The presence of cytomegalic cells, loss of vestibular hair cells, and degeneration of vestibular nerve fibers was also analyzed in the vestibular end organs. This analysis included the counting of cytomegalic cells in temporal bone sections. Cytomegalic cells were assessed at a magnification of 400× in areas of their high density in the cochlear duct or in the location of dark cells in the vestibular labyrinth (per area).

RESULTS

We analyzed 4 temporal bones from 3 newborn infants with cCMV infection (Cases 1-3) to evaluate these bones for pathological changes in the cochlear and vestibular labyrinths. As

a controls, we used human temporal bones from children without CMV or other ear diseases. We noted in the typical control sample (from a 15-year-old girl) that the cochlear epithelium shows intact inner (IHC) and outer (OHC) hair cells in the organ of Corti (Figure 1a); and the vestibular epithelium shows vestibular hair cells, dark cells, and transitional cells in the lateral semicircular canals (Figure 1b).

Case 1: Right temporal bone

No large cytomegalic cells were found in the cochlear and vestibular labyrinths. The organ of Corti demonstrated a normal appearance with the presence of both outer (OHC) and inner (IHC) hair cells (arrows) in the basilar turn of the cochlear duct. The Reissner's membrane was seen collapsed on tectorial membrane (Figure 2a). The spiral ganglion showed no apparent lesions. A few disintegrated cells (arrow) were seen near the spiral prominence area of the stria vascularis. In contrast to endolymphatic space, there were large areas of stained material in the perilymphatic space of the scala tympani. A high power view of the boxed area (Figure 2a, inset) showed rounded cells with nuclei (arrows), lysed cells, and one neutrophil (arrowhead). No similar stained material was observed in the vestibular labyrinth. Sensory hair cells in the vestibular labyrinth showed a presence of type 1 and 2 cells in the macula of the utricle and saccule (Figure 2b). No loss of vestibular hair cells, dark cells, transitional cells, and nerve fibers (arrow) was observed in the semicircular canals (Figure 2c).

Case 2: Left temporal bone

The normal appearance of inner and outer hair cells in the organ of Corti was observed (Figure 3a). The hypervascularization was visible in the stria vascularis in all cochlear turns. There was a local deterioration of marginal cell integrity in the stria vascularis; in addition, some strial cells were detached into endolymphatic space (Figure 3a, open arrows). Compared to control non-diseased temporal bones, vestibular end organs of this patient demonstrated a loss of type 1 and 2 hair cells in the macula of utricle and saccule, severe loss of vestibular hair cells, and degeneration of nerve fibers (arrow) in the semicircular canals (Figure 3b). We analyzed in the inner ear the presence of large, inclusion-bearing cytomegalic cells that are most often associated with CMV infection (Figure 3b,c). Large clusters of cytomegalic cells (Figure 3c, arrowheads) were mostly located in the area of dark cells. There were also some cytomegalic cells on the wall of the vestibular labyrinth.

Case 2: Right temporal bone

Compared to the left temporal bone of the same Case 2, no evidence of cytomegalic cells was found in the cochlea or vestibular labyrinth in the right temporal bone of this patient. A loss of outer hair cells (Figure 4a, arrow) was observed in the organ of Corti. The stria vascularis showed hypervascularization and enlarged blood vessels in all cochlear turns; there was also loss of cells and edema, most noticeable in the layer of intermediate cells. Some cells separated from the the stria vascularis (Figure 4a, open arrow) were visible in the cochlear duct. The sensory epithelium of the vestibular system showed no loss of type 1 and 2 hair cells or other apparent abnormalities in the macula of the utricle (Figure 4b), saccule, and semicircular canals (Figure 4c).

Case 3: Right temporal bone

In contrast to Case 2, the temporal bone of this patient demonstrated cytomegalic cells with inclusion bodies in both cochlear and vestibular labyrinths. There was some degree of postmortem lytic changes in this temporal bone; partial atrophy and disruption of the stria vascularis was also observed. Cytomegalic cells were mainly observed in the upper cochlear turn. The tectorial membrane was collapsed on the organ of Corti. Cytomegalic cells (Figure 5a, arrowheads) were mostly attached to the endolymphatic side of Reissner's membrane and one cell was located beneath the basilar membrane. No cytomegalic cells were found within the organ of Corti and the stria vascularis. A high power image of the organ of Corti demonstrated a loss of outer hair cells (Figure 5b, arrow) and displacement of inner hair cells. The sensory epithelium in the vestibular system showed a loss of type 1 and 2 hair cells in the macula of the utricle (Figure 5c, asterisks; ~ 25% of hair cells are missed) and saccule. In Figure 5c, ~25% of hair cells are missed. There was also a loss of hair cells (Figure 5d, open arrow) and degeneration of nerve fibers in the semicircular canals. A large number of cytomegalic cells (5d, arrowheads) were found in the vestibular labyrinth, particular in the dark cells area of all three semicircular canals and on the inferior utricular crest, which is enriched for dark cells.

The hallmark of CMV infection is enlarged cytomegalic cells with inclusion bodies. In the cochlea pathological changes, such

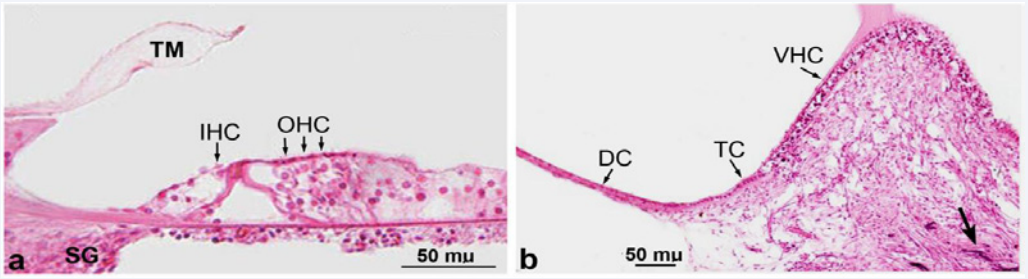

Figure 1 Representative images of control, non-diseased temporal bones showing sensory epithelium of the cochlear and vestibular labyrinths. a: The organ of Corti. IHC = inner hair cells; OHC = outer hair cells; TM = tectorial membrane; SG = spiral ganglion.
b: The crista of the lateral semicircular canal. VHC = vestibular hair cells; DC = dark cells; TC = transitional cells. Arrow shows vestibular nerve. Hematoxylin and eosin staining.

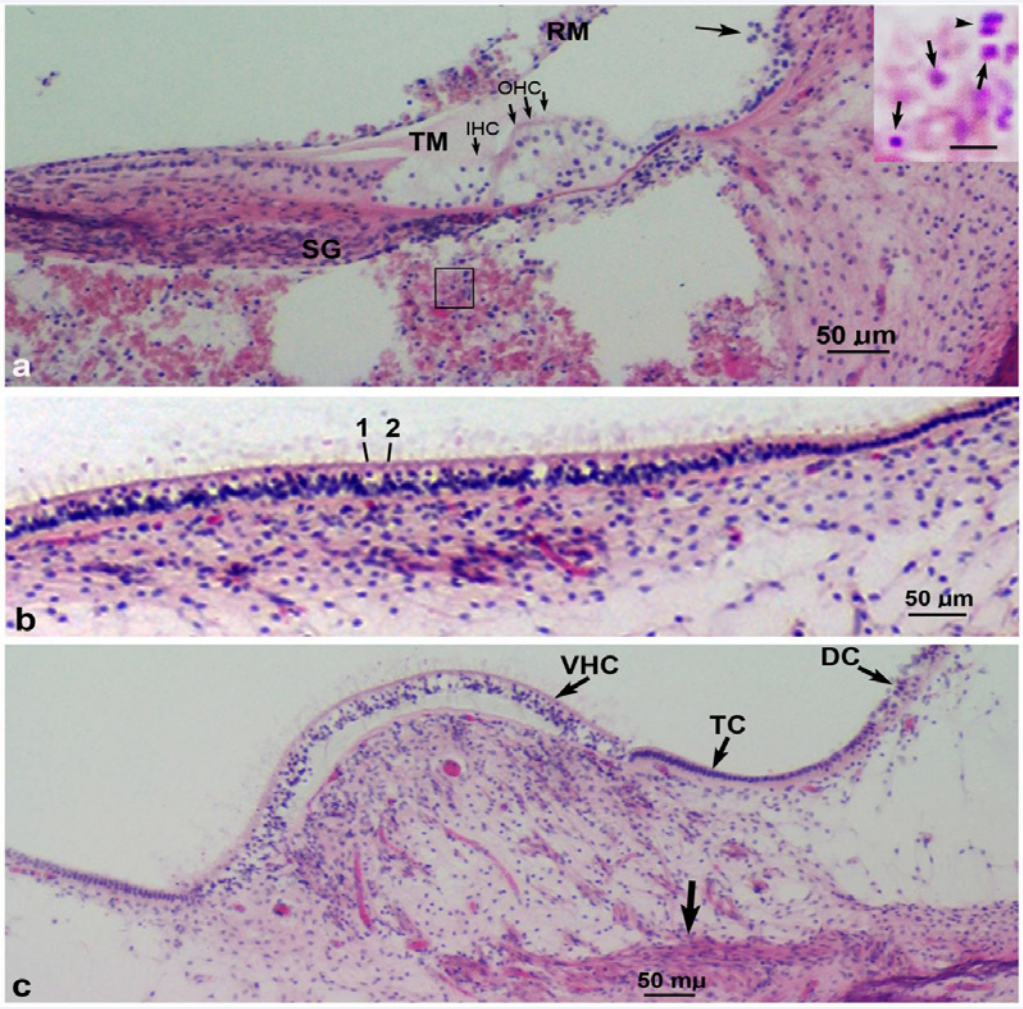

Figure 2 Right temporal bone of a 2-month 24 day-old girl with CMV infection. a: The organ of Corti shows normal appearance. Arrow indicates disintegrated cells near the spiral prominence area of the stria vascularis. A large area of stained material was observed in the scala tympani of the perilymphatic space. A high power view of the boxed area (a, inset; bar = 10 µm) shows rounded cells (arrows), lysed cells, and a single neutrophil (arrowhead). IHC = inner hair cells; OHC = outer hair cells; RM = Reissner's membrane; SG = spiral ganglion. b,c: Vestibular hair cells were intact with the presence of type 1 and type 2 cells in the macula of saccule (b) and in the lateral semicircular canal (c). VHC = vestibular hair cells; DC = dark cells; TC = transitional dark. Arrow shows nerve fibers. Hematoxylin and eosin staining.

as loss or damage of hair cells, can be seen in Case 3 or without presence of cytomegalic cells (Cases 1 and 2). In temporal bone of Case 3 (Fig. 5a), a few epithelial cells of Reissner's membrane containing cytomegalic inclusions are seen on the surface lined the scala media. In vestibular system of the temporal bones in Case 2 (Figure 3c) and in Case 3 (Figure 5b) severe loss hair cells and degeneration of nerve fibers is associated with the presence of large number of cytomegalic cells in the areas of dark cells. This fact also points out that a loss of hair cells is caused primarily by CMV infection and not by postmortem autolysis of temporal bones.

Table 1 summarizes the prominent cochleovestibular histopathologies in 4 human temporal bones examined in one or both ears of 3 newborn infants with cCMV infection.

DISCUSSION

The inner ear plays the most significant role in the pathogenesis of CMV-induced hearing loss and vestibular disorders. In this study, the cochlear and vestibular histopathologies were examined in 4 temporal bones from 3 newborn infants with cCMV infection (Cases 1-3). All infants were symptomatic with cCMV and represent a severely affected population, while the majority of newborns are asymptomatic. We found significant differences in the presence of cytomegalic cells and structural damage in both cochlear and vestibular parts of the inner ear between all 4 temporal bones. In particular, no cytomegalic cells was observed in the temporal bone of Case 1. Large areas of cellular and non-cellular structures were observed in the scala tympani of the perilymphatic space; however, there was no obvious loss of cochlear and vestibular hair cells. In Case 2, cytomegalic cells in the area of dark cells and a loss of vestibular type 1 and 2 hair cells was observed only in the vestibular labyrinth of the left temporal bone; and a loss of cochlear hair cells was visible only in the right temporal bone. The temporal bone of Case 3 showed cytomegalic cells in the cochlear duct and vestibular labyrinth

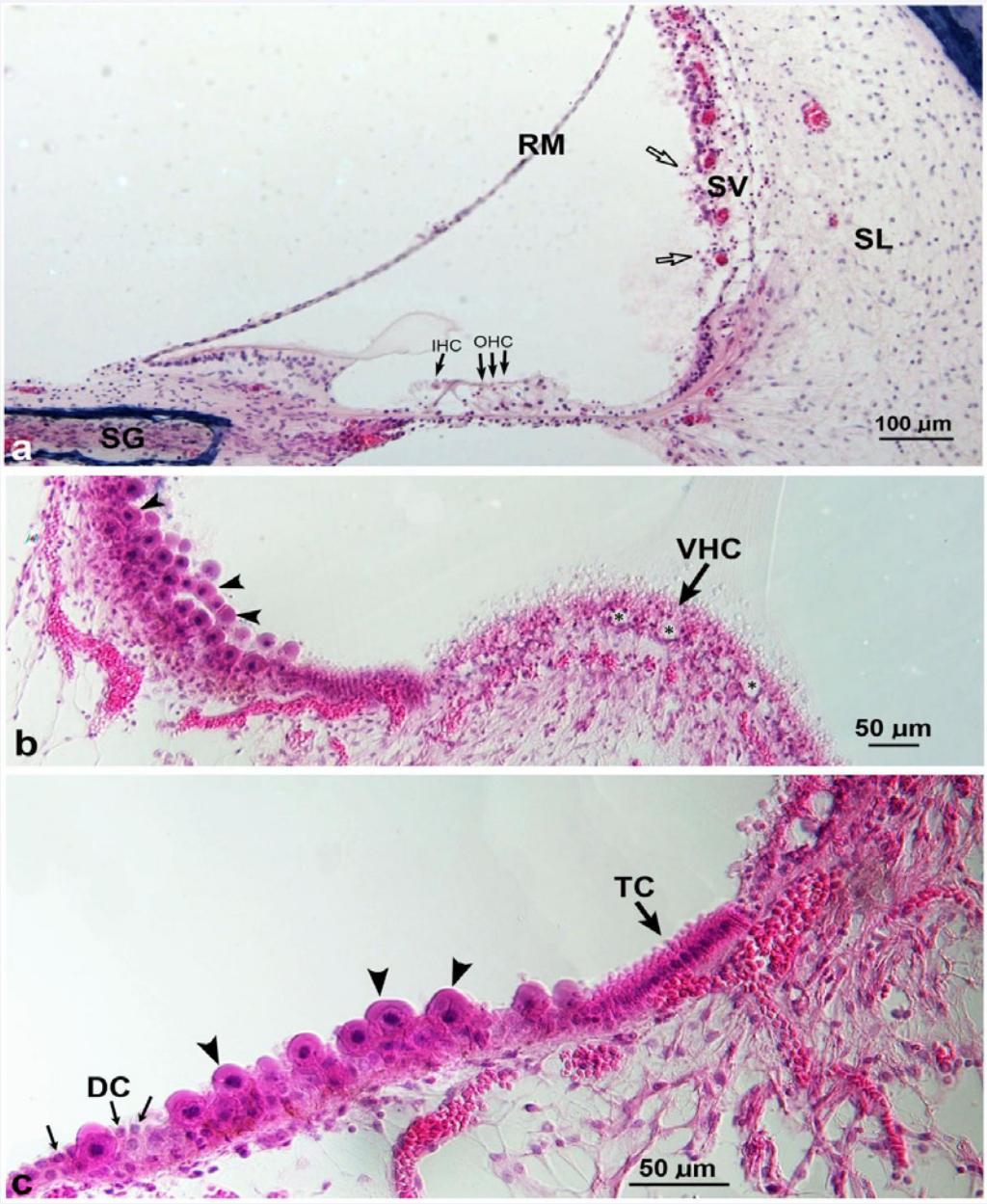

Figure 3 Case 2. a: Left temporal bone of this 11-day-old boy with cCMV infection shows normal appearance of both outer and inner hair cells in the organ of Corti. There was a hypervascularization in the stria vascularis; some strial cells were detached into endolymphatic space (open arrows). IHC = inner hair cells; OHC = outer hair cells; SV = stria vascularis; SG = spiral ganglion. b,c: In the vestibular labyrinth, large clusters of inclusion-bearing cytomegalic cells (arrowheads), were mostly located on the dark cells. A severe loss (asterisks) of vestibular hair cells and degeneration of nerve fibers (arrow) in the lateral semicircular canal (b). VHC = vestibular hair cells. DC = dark cells. TC = transitional cells. Hematoxylin and eosin staining.

with a loss of hair cells in the organ of Corti and vestibular system that can be a potential source of the SNHL and vestibular disorders, respectively. There were more cytomegalic cells, hair cells loss, the degeneration of nerve fibers, and other lesions in the vestibular system than in the cochlea. More severe structural lesions in the vestibular system compared to the cochlea were also reported in newborn infants with CMV infection by other authors [18,19]. These studies also demonstrated a high concentration of cytomegalic cells associated with dark cells, loss of hair cells in the macula of the vestibular end organs, and degeneration of nerve fibers. In contrast, in fetal human temporal bones, the vestibular stuctures were found less infected by CMV compared to the cochlea [22]. Auditory and vestibular hair cells are involved in mechanoelectrical transduction [25]. Both types of the sensory cells are dependent on potassium flux. Dark cells are secretory cells functionally similar to marginal cells of the stria vascularis; they transport potassium ions into the inner ear endolymph, whose homeostasis is essential for hearing and balance [26,27]. The loss of vestibular hair cells and nerve fibers in temporal bones is consistent with vesibular tests, showing frequent and

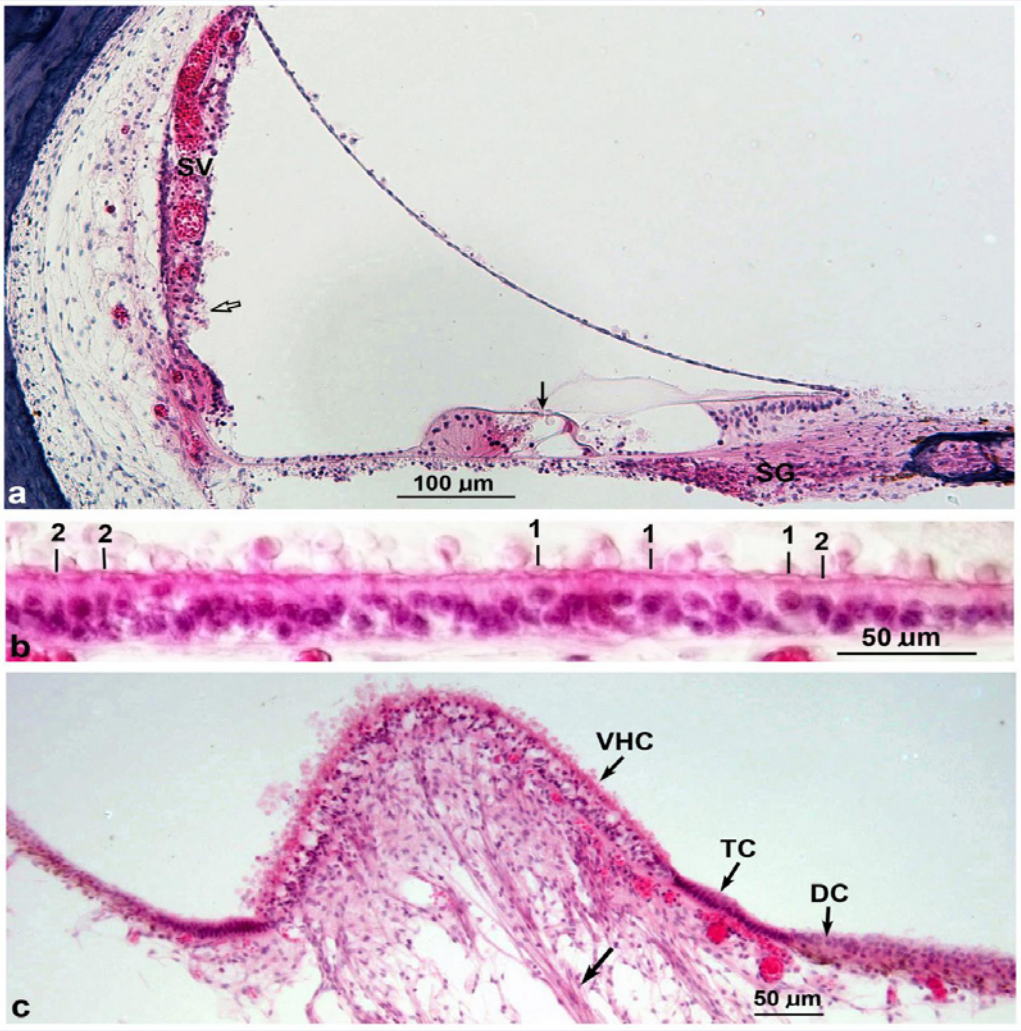

Figure 4 Case 2. Right temporal bone. a: Compared to the left temporal bone of the same infant (Fig. 3), no evidence of cytomegalic cells was found in its inner ear. A loss of outer hair cells (arrow) was observed in the organ of Corti. The stria vascularis showed hypervascularization and enlarged blood vessels in all cochlear turns. Separated strial cells (open arrow) are visible in the cochlear duct. IHC = inner hair cells; OHC = outer hair cells; SV = stria vascularis; SG = spiral ganglion. b,c: The sensory epithelium in the vestibular system showed intact type 1 and 2 hair cells in the macula of the utricle (b) and lateral semicircular canal (c). VHC = vestibular hair cells. DC = dark cells. TC = transitional cells. Hematoxylin and eosin staining.

Table 1: Histological findings in the temporal bones of newborns (Cases 1-3) with cCMV.

Case/ Ear	Age/ Sex	Cochlea	Vestibular system	Cytomegalic cells/per area	
				Cochlear duct	Vestibular system
1 Right	12 weeks F	No loss of hair cells Large areas of cells and non-cellular components in scala tympani	No loss of vestibular hair cells No degeneration of nerves	0	0
2 Left	11 days M	No loss of hair cells Hypervascularity of stria vascularis	Severe loss of vestibular hair cells Degeneration of nerves	0	20
2 Right		Loss or damage of outer hair cells Hypervascularity of stria vascularis	No loss of vestibular hair cells No degeneration of nerves	0	0
3 Right	21 days F	Loss or damage of outer hair cells	Severe loss of vestibular hair cells Degeneration of nerves	5	26

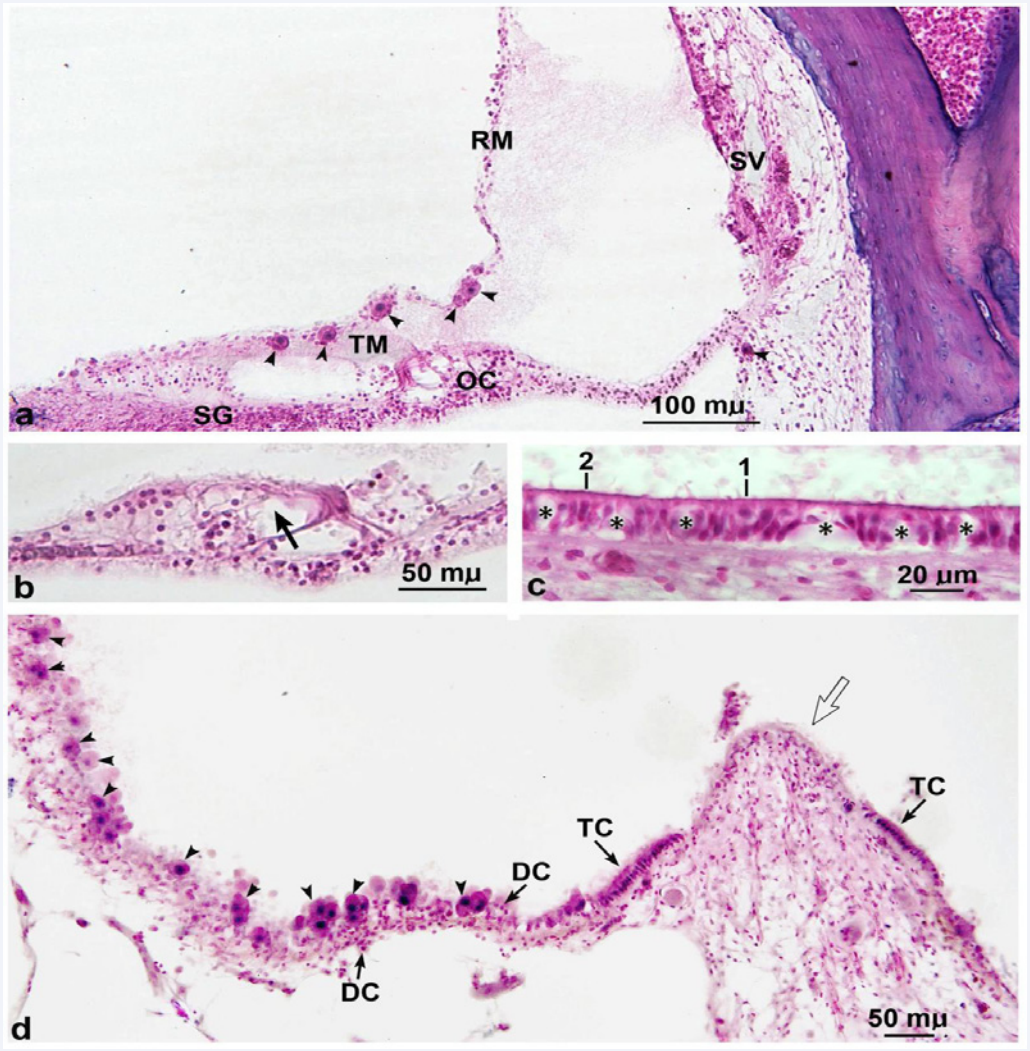

Figure 5 Case 3. a: Right temporal bone of this a 3-week-old girl with cCMV infection shows cytomegalic cells with inclusion bodies in both cochlear duct and vestibular labyrinth. Cytomegalic cells (arrowheads) were mostly attached to the endolymphatic side of the Reissner's membrane. b: A high power image of the organ of Corti showing a loss of outer hair cells (arrow). OC = Organ of Corti. TM = tectorial membrane; RM = Reissner's membrane; SG = spiral ganglion; SV = stria vascularis. c: The vestibular system shows a loss of type 1 and 2 hair cells (asterisks) in the utricular macula. d: A loss of vestibular hair cells (open arrow) and nerve fibers in the posterior semicircular canal. Large number of cytomegalic cells (arrowheads) was in the dark cells area of the canal. DC = dark cells. TC = transitional cells. Hematoxylin and eosin staining.

often severe vestibular impairment in cCMV infection that may progress independently of hearing loss [8,9,28,29]. In prospective study [10] of 93 enrolled children with a confirmed diagnosis of cCMV (52 asymptomatic, 41 symptomatic), 17 (18%) patients had SNHL (7 unilateral, 10 bilateral). Vestibular loss was detected in 13 (14%) patients (7 unilateral, 6 bilateral).

The diversity of cochlear and vestibular histopathologies, underlying the variable hearing loss and vestibular disorders in newborns with cCMV, can be directly associated with different routes of infection, viral load, and timing of cochlear infection and/or the vestibular system. In the early stages of viremia, virus can directly enter the inner ear from the blood and affect the integrity of the blood-labyrinth barrier. Other possible routes of virus invasion include the spiral ganglion, cochlear aqueduct from the subarachnoid space, and the round window membrane of the middle ear [30]. The routes of CMV inoculation used in experimental animal models and the immune status of the host may also be related to some differences in the inner ear pathologies observed in animal models and human temporal bones

CONCLUSION

Human temporal bones of newborns with cCMV demonstrate diverse cochleovestibular histopathologies. This diversity is consistent with the variable SNHL and vestibular dysfunction reported in infected newborns.

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CONFLICT OF INTEREST

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REFERENCES

1. Britt WJ. Cytomegalovirus. In: Remington JS, Klein JO, Wilson CB, Nizet V, Maldonado Y, editors. Infectious Diseases of the Fetus and Newborn Infant. Philadelphia: Elsevier Saunders, 2011; 706-755.
2. Dollard SC, Schleiss MR, Grosse SD. Public health and laboratory considerations regarding newborn screening for congenital cytomegalovirus. J Inherit Metab Dis. 2010; 33: S249-254.
3. Fowler KB. Congenital cytomegalovirus infection: audiologic outcome. Clin Infect Dis. 2013; 57: S182-84.
4. Goderis J, De Leenheer E, Smets K, et al. Hearing Loss and Congenital CMV Infection: A Systematic Review. Pediatrics. 2014; 134: 972-982.
5. Kimberlin DW, Lin CY, Sanchez PJ, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. J Pediatr. 2003; 143: 16-25.
6. Kimberlin DW, Jester PM, Sanchez PJ, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. N Engl J Med. 2015; 372: 933-943.
7. Schleiss MR, Diamond DJ. Exciting Times for Cytomegalovirus (CMV) Vaccine Development: Navigating the Pathways toward the Goal of Protecting Infants against Congenital CMV Infection. Vaccines (Basel). 2020; 8: 526.
8. Zagólski O. Vestibular-evoked myogenic potentials and caloric stimulation in infants with congenital cytomegalovirus infection. J Laryngol Otol. 2008; 122: 574-579.
9. Karltorp E, Lofkvist U, Lewensohn-Fuchs I, Ilona Lewensohn-Fuchs, Katarina Lindström, Mimmi Eriksson Westblad, Kristina Teär Fahnehjelm, Luca Verrecchia, et al. Impaired balance and neurodevelopmental disabilities among children with congenital cytomegalovirus infection. Acta Paediatr. 2014; 103: 1165-1173.
10. Dhondt C, Maes L, Lotte R, Sarie Martens, Saartje Vanaudenaerde, Helen Van Hoecke, et al. Vestibular Function in Children With a Congenital Cytomegalovirus Infection: 3 Years of Follow-Up. Ear Hear. 2020; 42: 76-86.
11. Schachtele SJ, Mutnal MB, Schleiss MR, Lokensgard JR. Cytomegalovirus-induced sensorineural hearing loss with persistent cochlear inflammation in neonatal mice. J Neurovirol. 2011; 17: 201-211.
12. Bradford, RD, Yoo YG, Golemac M, Ester Pernjak Pugel, Stipan Jonjic, William J Britt, et al. Murine CMV-induced hearing loss is associated with inner ear inflammation and loss of spiral ganglia neurons. PLoS Pathog. 2015; 11: e1004774.
13. Carraro M, Almishaal A, Hillas E, Matthew Firpo, Albert Park, Robert V Harrison, et al. Cytomegalovirus (CMV) infection causes degeneration of cochlear vasculature and hearing loss in a mouse model. J Assoc Res Otolaryngol. 2017; 18: 263-273.
14. Mattes FM, McLaughlin JE, Emery VC, DA Clark, PD Griffiths. Histopathological detection of owl's eye inclusions is still specific for cytomegalovirus in the era of human herpesviruses 6 and 7. J Clin Pathol. 2000; 53: 612-624.
15. Myers EN, Stool S. Cytomegalic inclusion disease of the inner ear. Laryngoscope. 1968; 78: 1904-1915.
16. Keithley M, Sharp P, Woolf NK, Harris JP. Temporal sequence of viral antigen expression in the cochlea induced by cytomegalovirus. Acta Otolaryngol. 1988; 106: 46-54.
17. Stagno S, Reynolds DW, Amos CS, Dahle AJ, Faye P. McCollister FP, Mohindra I, et al. Auditory and Visual Defects Resulting from Symptomatic and Subclinical Congenital Cytomegaloviral and Toxoplasma Infections. Pediatrics. 1977; 59: 669-678.
18. Davis LE, Johnsson LG, Kornfeld M. Cytomegalovirus labyrinthitis in an infant: morphological, virological, and immunofluorescent studies. J Neuropathol Exp Neuro. 1981; 40: 9-19.
19. Strauss M. Human cytomegalovirus labyrinthitis. Review. Am J Otolaryngol. 1990; 11: 292-298.
20. Schuknecht HF. Pathology of the ear. Philadelphia: Lea and Febiger, 1993. 326-327.
21. Teissier N, Delezoide AL, Anne-Elisabeth Mas, Suonavy Khung-Savatovsky, Bettina Bessières, Jeannette Nardelli, et al. Inner ear lesions in congenital cytomegalovirus infection of human fetuses. Acta Neuropathol (Berl). 2011; 122: 763-774.
22. Gabrielli L, Bonasoni MP, Santini D, Giulia Piccirilli, Angela Chiereghin, Brunella Guerra, et al. Human fetal inner ear involvement in congenital cytomegalovirus infection. Acta Neuropathol Commun. 2013; 1: 63-71.
23. Tsuprun V, Keskin N, Schleiss MR, Pat Schachern, Sebahattin Cureoglu. Cytomegalovirus-induced pathology in human temporal bones with congenital and acquired infection. Am J Otolaryngol. 2019: 40: 102270.
24. Davis LE, Rarey KE, Stewart JA, McLaren LC. Recovery and probable persistent of cytomegalovirus in human inner ear fluid without cochlear damage. Ann Otol Rhinol Laryngol. 1987; 96: 380-383.
25. Gillespie PG, Müller U. Mechanotransduction by Hair Cells: Models, Molecules, and Mechanisms. Cell. 2009; 139: 33-44.
26. Kimura RS. Distribution, structure, and function of dark cells in the vestibular labyrinth. Ann Otol Rhinol Laryngol. 1969; 78: 542-561.
27. Ciuman RR. Stria vascularis and vestibular dark cells: characterization of main structures responsible for inner-ear homeostasis, and their pathophysiological relations. J Laryngol Otol. 2009; 123: 151-162.
28. Bernard S, Wiener-Vacher S, Van Den Abbeele T, Teissier N. Vestibular disorders in children with congenital cytomegalovirus infection. Pediatrics. 2015; 136: e887-895.
29. Teissier N, Bernard S, Quesnel S, Van Den Abbeele T. Audiovestibular consequences of congenital cytomegalovirus infection. Eur Ann Otorhinolaryngol Head Neck Dis. 2016; 133: 413-418.
30. Xia W, Yan H, Zhang Y, Wang C, Wei Gao, Changning Lv, Wentao Wang, et al. Congenital Human Cytomegalovirus Infection Inducing Sensorineural Hearing Loss. Front Microbiol. 2021; 12: 649690.