Acquired Cytomegalovirus Infection Hearing Loss

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Congenital cytomegalovirus (CMV) infection induces a clinical syndrome usually associated with hearing loss. However, the effect of acquired CVM infection in adults and children has not been clearly defined.

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1. Introduction

The human cytomegalovirus (CMV) is a DNA virus included in the herpesviridae family, widely spread in the community. Subclinical infections do occur and they can involve all bodily organs, including the middle and the inner ear. Congenital CMV infection can produce a wide variety of clinical syndromes either by direct pathogenic effect or secondary to immune mechanisms. Acquired CMV infection is asymptomatic in most adults; however, it can produce severe symptoms in patients with compromised immune system [1].

Much of the pathogenesis associated with congenital CMV infection is explained by the virus' ability to establish a latent infection in the host. In its latent state, the viral genome is maintained in the host cell without active replication; however, CMV is able to reactivate itself in response to changes in the host cell [2]. CMV persists for the lifetime of the infected host leading to a latent chronic infection, in which only a limited number of viral genes are expressed without genome replication. Cellular death pathways that are activated by viral infection as well as other biological processes, including control of the cell cycle and cellular stress responses, are efficiently regulated by CMV in the infected cell to facilitate virus replication. CMV has a broad cellular tropism and infects a large number of cell types during primary infection; however, the outcome of infection varies widely and is largely cell type-dependent and it may include endothelial, epithelial, fibroblasts, neuronal, monocytes/macrophages, granulocytes, and smooth muscle cells [3].

The histopathological damage of CMV disease was reported in 41 temporal bones of children with acquired CMV infection in a non-controlled study [4]. Typical inclusion bodies of CMV, namely multiple vacuoles with clusters of viral particles within the nucleus of affected cell was contained in the epithelium of the endolymphatic sac, the utricle, and the semicircular canals; there was loss of inner and outer hair cells, and of cochlear ganglion cells [5]. It has been postulated that many ear disorders, including Meniere's disease (MD) [6], otosclerosis [7] and sensorineural hearing loss (SNHL) of various forms may have an underlying viral etiology. CMV could damage the inner ear leading to endolymphatic hydrops in immune-mediated inner-ear disease [8][9]. Moreover, it is plausible

that CMV infection induces via pro-inflammatory state SNHL and tinnitus [10]. Among children with congenital CMV infection, the onset of deafness can occur in childhood even up to 6–8 years of life [8].

The seroprevalence of CMV differs greatly among different countries ranging from 50% up to 90% according to several factors, such as ethnicity or socio-economic status [11]. The prevalence of viral infection can be ascertained through various methods, including classical virological techniques such as transmission-electron microscopy, viral culture, or more recent methods offering comparably higher sensitivity, specificity, and throughput, sometimes broadly labeled as the 'molecular-diagnostics' of viral-infection [10]. Detection of CMV DNA can vary depending on the methods of DNA extraction [12], DNA amplification [13] and the part of the CMV genome being detected [14]. To confirm viral exposure in patients and control subjects, molecular ascertainments have been classified as those that aimed to (i) directly detect specific viral species through their nucleic acid or gene products (active or latent infection), or else (ii) indirectly detect specific viral exposures through antiviral antibody signatures of past or recent infection [10]. Prospective studies of CMV antibody including 2572 healthy blood donors have disclosed that between 40 and 100% of them have antibodies to CMV. Positive results of serologic tests presumably may reflect a latent congenital CMV infection [15][16].

While the precise mechanism of progressive hearing loss mediated by CMV infection is unknown, there are two possible mechanisms that would explain the clinical course: (1) the direct damage of hair cells or spiral ganglion neurons by a persistent acquired CMV infection, and (2) the host immune mediated CMV damage of infected cells [17]. The finding of CMV DNA in the inner ear fluids of children allowed to assume that this virus can not only injure the inner ear when acquired in pre-and perinatally age, but also later on [18] The main mechanism of SNHL in CMV congenital infection may be the alteration of potassium homeostasis via damage to the stria vascularis or Reissner's membrane, with secondary damage to the organ of Corti. This mechanism can be also suggested for non-congenital infection since the virus is known to prefer undifferentiated cells (such as stem cells) [19].

The involvement of viruses in the pathogenesis of SNHL has been suggested by investigations conducted on animal models as well as from clinical, serologic, and histopathologic data collected on patients with acute idiopathic hearing loss. Several studies suggest that patients with SNHL, especially those with sudden onset [20], could be the result of a viral infection and Herpesviridae are currently considered the most likely etiological factor. A particular cochlear tropism of CMV has been reported in post-mortem inner ear of an immunocompromised patient who died from the complications of acquired disseminated infection by CMV [5].

There are many studies showing an association between congenital CMV infection and SNHL; however, the evidence to support an acquired CMV infection is limited. Most CMV infections have few symptoms and the inner ear damage associated with SNHL may be delayed, the causality being difficult to demonstrate.

2. The Association of Acquired Human Cytomegalovirus Infection with Hearing Loss

The first report describing an association of acquired CMV infection with SNHL was published 40 years ago; however, the pathogenic mechanism of hearing loss is not fully understood. Our systematic review shows that acquired CMV infection demonstrated by PCR or ELISA is not significantly associated with SNHL in adults or children and the evidence to support an association between acquired CMV infection and SNHL is weak.

We have identified nine case-control studies to assess the association between acquired CMV infection in adults or children and SNHL. However, only six studies resulted appropriate to calculate the pooled OR. Among these studies, the frequency of SNHL in individuals with acquired CMV infection was slightly higher (19.78%) compared to the frequency of CMV infected individuals without SNHL (15.86%). However, given that only six studies could be selected for the metanalysis and the study of Verbeeck et al. [21] contributed with 48% of the individuals, we cannot rule out a bias. Overall, according to the meta-analysis, CMV shows no association with SNHL, while the association with tinnitus has not been investigated. For viral infection diagnosis, PCR and ELISA tests were the most used methods in these reports. The variability of the audiological profile of the CMV infected patients can result from a broad possibility of causes of hearing loss. Among them: the clinical condition of the patients, making them susceptible to numerous opportunistic infections, ototoxic drugs, and the action of the virus itself.

Four of the selected studies reported hearing thresholds. Two studies [22][23] described the same hearing thresholds (<40 dB) in case and control groups. However, the other two studies [24][25] showed differences among the case (mean 78 dB) and control groups (mean 60 dB). Paryani et al. reported a high frequency SNHL (>4000 dB) in all cases. Unfortunately, none of the studies included information about the age of onset of SNHL.

An examination of human temporal bones along with studies of animal models indicates that CMV (or a CMV protein) may be present in the sensorineural epithelium and the spiral ganglion neurons. This may cause damage to the inner ear by virus-mediated damage to hair cells, supporting cells or neurons, and/or secondary to host-derived inflammatory responses to CMV in the ear, resulting in injury to the cochlea and hearing loss [15]. However, this hypothesis does not fully explain the progressive and late-onset nature of CMV-related hearing loss. How CMV is related to the pathogenesis of SNHL is not known, and limited audiological assessment in patients with confirmed congenital CMV infection has been performed in most studies to determine if the primary damage occurs at the organ of Corti or the auditory nerve fibers. Moreover, CMV may affect the inner ear by several mechanisms that might include: (a) labyrinthitis secondary to a viremia, (b) labyrinthitis or neuritis secondary to meningitis, (c) a cranial polyneuropathy, (d) reactivation of a latent infection in spiral ganglion neurons, or e) alteration of the cellular immune response [3].

As a result of molecular mimicry between viruses and inner ear tissues, humoral and/or cellular immune responses in the endolymphatic sac or the cochlea could cause auditory and/or vestibular pathologies. Mechanisms for inner ear injury may be influenced by temporary alterations in cellular immunity secondary to simultaneous viral infections as well as the virulence of CMV. To define a virus as an etiologic agent for hearing loss, three criteria should be satisfied: (1) successful isolation of the virus from the perilymph or endolymph, (2) morphological identification of the virus in cochlear cells by electron microscopy or by characteristic cytopathological changes, and (3) detection of viral antigen in the cochlear cells by immunohistochemical analysis [12]. These criteria are

difficult to fulfill in human cases, as hearing loss is not fatal and the encasement of the inner ear in dense temporal bone makes it difficult to study in vivo. Collecting appropriate samples from the inner ear of a living subject for virus isolation purposes would require considerable technical skill and has a low (but significant) risk of permanent deafness. Recently, cochlear implants have become the established therapeutic method for treating SNHL, and it is now possible to collect perilymph at surgery [17].

Acquired CMV infection of the inner ear might be associated with SNHL, but evidence to support causality in the pathogenesis of hearing loss in children or adults is limited. The cochlear lesions in congenital CMV infection are diffuse, but predominate in the stria vascularis in a mouse model [26]. The stria vascularis is one of the most highly vascularized covering and lining epithelia found in mammals and the only one containing intra-epithelial vessels. The CMV may therefore penetrate the inner ear by this route and infect the marginal epithelial cells [19]. Nevertheless, histopathological studies are limited in adults [27].

Active infection and inflammation were also found in the saccule and utricle, predominantly in the non-sensory epithelial cells such as the transitory cells and dark cells. Active CMV replication was noted in the inner ear epithelial cells, mesenchymal tissue, and bone marrow cells, but not in the highly differentiated neurons or sensorineural cells, according to experimental data [27]. In any case, establishing whether a virus (or another infectious agent) is relevant in the pathophysiology of a neurotological condition involves a claim beyond the plausibility of virulence and a significant association [28].

Some data show that congenital CMV-related hearing loss is associated with ongoing viral replication in the inner ear several years later after birth [29]. However, some reports have investigated the relationship between congenital CMV infection and hearing impairment. The discovery of viral DNA in the perilymph of three of the subjects enrolled in these studies provided an in vivo demonstration that Herpesviruses could be isolated in the inner ear when it occurs in postnatal age [30][31].

There is an ongoing debate about the etiology and pathophysiology of SNHL in adults. In particular, an extensive disagreement exists regarding the role of different viruses in the onset of idiopathic sudden SNHL. The most accepted cause of SNHL, regardless of the patient's age, is viral labyrinthitis [23]. The finding of a prior viral infection in as many as 30–40% of SNHL patients presumably support this statement. However, several studies using conventional viral diagnostic tests have not confirmed that a viral infection is a common cause of SNHL [32]. According to the limited evidence, 60% of individuals without SNHL have antibodies anti-CMV IgG [33].

References

1. Vancíková, Z.; Dvorák, P. Cytomegalovirus infection in immunocompetent and immunocompromised individuals—A review. Curr. Drug Targets Immune Endocr. Metab. Disord. 2001, 1, 179–187.

2. Dupont, L.; Reeves, M.B. Cytomegalovirus latency and reactivation: Recent insights into an age old problem. Rev. Med. Virol. 2016, 26, 75–89.
3. Poole, E.; Walther, A.; Raven, K.; Benedict, C.A.; Mason, G.M.; Sinclair, J. The myeloid transcription factor GATA-2 regulates the viral UL144 gene during human cytomegalovirus latency in an isolate-specific manner. J. Virol. 2013, 87, 4261–4271.
4. Myers, E.N.; Stool, S. Cytomegalic Inclusion Disease of the Inner Ear. Laryngoscope 1968, 78, 1904–1915.
5. Bachor, E.; Sudhoff, H.; Litschel, R.; Karmody, C.S. The pathology of the temporal bones of a child with acquired cytomegalovirus infection: Studies by light microscopy, immunohistochemistry and polymerase-chain reaction. Int. J. Pediatric Otorhinolaryngol. 2000, 55, 215–224.
6. Schuknecht, H.F.; Suzuka, Y.; Zimmermann, C. Delayed endolymphatic hydrops and its relationship to Ménière's disease. Ann. Otol. Rhinol. Laryngol. 1990, 99, 843–853.
7. McKenna, M.J.; Kristiansen, A.G.; Haines, J. Polymerase chain reaction amplification of a measles virus sequence from human temporal bone sections with active otosclerosis. Am. J. Otolaryngol. 1996, 17, 827–830.
8. Kamei, T. Delayed Endolymphatic Hydrops as a Clinical Entity. Int. Tinnitus J. 2004, 10, 137–143.
9. Lobo, D.; Tuñon, M.; Villarreal, I.; Brea, B.; Garcıa-Berrocal, J.R. Intratympanic gadolinium magnetic resonance imaging supports the role of endolymphatic hydrops in the pathogenesis of immune-mediated inner-ear disease. J. Laryngol. Otol. 2018, 132, 554–559.
10. Dean, N.J.; Pastras, C.; Brown, J.D.; Camp, A.J. Are viral-infections associated with Me´nière's Disease? A systematic review and metaanalysis of molecular-markers of viral-infection in case-controlled observational studies of MD. PLoS ONE 2019, 14, e0225650.
11. Cannon, M.J.; Schmid, D.S.; Hyde, T.B. Review of cytomegalovirus seroprevalence and demographic.characteristics associated with infection. Rev. Med. Virol. 2010, 20, 202–213.
12. Soetens, O.; Vauloup-Fellous, C.; Foulon, I.; Dubreuil, P.; De Saeger, B.; Grangeot-Keros, L.; Naessens, A. Evaluation of different cytomegalovirus (CMV) DNA PCR protocols for analysis of dried blood spots from consecutive cases of neonates with congenital CMV infections. J. Clin. Microbiol. 2008, 46, 943–946.
13. Barbi, M.; MacKay, W.G.; Binda, S.; van Loon, A.M. External quality assessment of cytomegalovirus DNA detection on dried blood spots. BMC Microbiol. 2008, 8, 2.
14. Atkinson, C.; Walter, S.; Sharland, M.; Tookey, P.; Luck, S.; Peckham, C.; Griffiths, P. Use of stored dried blood spots for retrospective diagnosis of congenital CMV. J. Med. Virol. 2009, 81, 1394–1398.

15. Bale, J.F., Jr. Human cytomegalovirus infection and disorders of the nervous system. Arch. Neurol. 1984, 41, 310–320.
16. Bayer, W.L.; Tegtmeier, G.E. The blood donor: Detection and magnitude of cytomegalovirus carrier states and the prevalence of cytomegalovirus antibody. Yale J. Biol. Med. 1976, 49, 5–12.
17. Sugiura, S.; Yoshikawa, T.; Nishiyama, Y.; Morishita, Y.; Sato, E.; Hattori, T.; Nakashima, T. Detection of human cytomegalovirus DNA in perilymph of patients with sensorineural hearing loss using real-time PCR. J. Med. Virol. 2003, 69, 72–75.
18. Di Nardo, W.; Cattani, P.; Lopizzo, T.; Cantore, I.; Marchese, M.R.; Marchetti, S.; Scorpecci, A.; Giannantonio, S.; Parrilla, C.; Cianfrone, F.; et al. Multiple viral genome search in endolabyrinthic fluids of profoundly deaf patients: Possible cytomegalovirus intracochlear reactivation. Audiol. Neurootol. 2009, 14, 290–295.
19. Teissier, N.; Delezoide, A.-L.; Mas, A.-E.; Khung-Savatovsky, S.; Bessières, B.; Nardelli, J.; Vauloup-Fellous, C.; Picone, O.; Houhou, N.; Oury, J.-F.; et al. Inner ear lesions in congenital cytomegalovirus infection of human fetuses. Acta Neuropathol. 2011, 122, 763–774.
20. Gross, M.; Wolf, D.G.; Elidan, J.; Eliashar, R. Enterovirus, cytomegalovirus, and Epstein-Barr virus infection screening in idiopathic sudden sensorineural hearing loss. Audiol. Neurotol. 2007, 12, 179–182.
21. Verbeeck, J.; Van Kerschaver, E.; Wollants, E.; Beuselinck, K.; Stappaerts, L.; Van Ranst, M. Detection of perinatal cytomegalovirus infection and sensorineural hearing loss in belgian infants by measurement of automated auditory brainstem response. J. Clin. Microbiol. 2008, 46, 3564–3568.
22. Jim, W.T.; Chiu, N.C.; Ho, C.S.; Shu, C.H.; Chang, J.H.; Hung, H.Y.; Kao, H.A.; Chang, H.Y.; Peng, C.C.; Yui, B.H.; et al. Outcome of Preterm Infants with Postnatal Cytomegalovirus Infection via Breast Milk: A Two-Year Prospective Follow-Up Study. Medicine 2015, 94, e1835.
23. Wilson, W.R. The relationship of the herpesvirus family to sudden hearing loss: A prospective clinical study and literature review. Laryngoscope 1986, 96, 870–877.
24. Kikidis, D.; Nikolopoulos, T.P.; Kampessis, G.; Stamatiou, G.; Chrysovergis, A. Sudden sensorineural hearing loss: Subclinical viral and toxoplasmosis infections as aetiology and how they alter the clinical course. ORL J. Otorhinolaryngol. Relat. Spec. 2011, 73, 110–115.
25. Paryani, S.G.; Yeager, A.S.; Hosford-Dunn, H.; Johnson, S.J.; Malachowski, N.; Ariagno, R.L.; Stevenson, D.K. Sequelae of acquired cytomegalovirus infection in premature and sick term infants. J. Pediatr. 1985, 107, 451–456.
26. Carraro, M.; Almishaal, A.; Hillas, E.; Firpo, M.; Park, A.; Harrison, R.V. Cytomegalovirus (CMV) Infection Causes Degeneration of Cochlear Vasculature and Hearing Loss in a Mouse Model. J. Assoc. Res. Otolaryngol. 2017, 18, 263–273.

27. Tsuprun, V.; Keskin, N.; Schleiss, M.R.; Schachern, P.; Cureoglu, S. Cytomegalovirus-induced pathology in human temporal bones with congenital and acquired infection. Am. J. Otolaryngol. 2019, 40, 102270.
28. Greco, A.; Gallo, A.; Fusconi, M.; Marinelli, C.; Macri, G.F.; de Vincentiis, M. Meniere's disease might be an autoimmune condition? Autoimmun. Rev. 2012, 11, 731–738.
29. Kato, K.; Otake, H.; Tagaya, M.; Takahashi, Y.; Ito, Y.; Hama, A.; Nakashima, T. Progressive hearing loss following acquired cytomegalovirus infection in an immunocompromised child. Am. J. Otolaryngol. Head Neck Med. Surg. 2013, 34, 89–92.
30. Vries, J.J.; Vesseur, A.; Rotteveel, L.J.; Korver, A.M.; Rusman, L.G.; Wessels, E.; Kroesa, A.C.M.; Mylanusb, E.A.; Oudesluys-Murphyd, A.M.; Frijns, J.H.M.; et al. Cytomegalovirus DNA detection in dried blood spots and perilymphatic fluids from pediatric and adult cochlear implant recipients with prelingual deafness. J. Clin. Virol. 2013, 56, 113–117.
31. Foulon, I.; Naessens, A.; Faron, G.; Foulon, W.; Jansen, A.C.; Gordts, F. Hearing thresholds in children with congenital CMV infection: A prospective study. Int. J. Pediatr. Otolaryngol. 2012, 76, 712–717.
32. Garcia Berrocal, J.R.; Ramírez-Camacho, R.; Portero, F.; Vargas, J.A. Role of viral and Mycoplasma pneumoniae infection in idiopathic sudden sensorineural hearing loss. Acta Oto-Laryngol. 2000, 120, 835–839.
33. Gkrania-Klotsas, E.; Langenberg, C.; Sharp, S.J.; Luben, R.; Khaw, K.-T.; Wareham, N.J. Seropositivity and higher immunoglobulin g antibody levels against cytomegalovirus are associated with mortality in the population-based European prospective investigation of cancer-norfolk cohort. Clin. Infect. Dis. 2013, 56, 1421–1427.