CMV Infection in Patients with Profound Hearing Loss

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Abstract
Our aim was to find out the prevalence of cytomegalovirus infection among the TORCH (toxoplasma, rubella, cytomegalovirus, herpes simplex) infections in children with profound sensorineural hearing loss (SNHL). Our study involved 140 patients who were presented to deafness clinic in ENT OPD of Pacific Medical college and Hospital, Udaipur between January 2014 and July 2018. Out of 140 patients, 107 had TORCH laboratory results. 60 were positive for cytomegalovirus (CMV) IgG antibody while 42 were positive for rubella IgG and 5 patients were positive for toxoplasmosis IgG antibodies. No patient showed positive results for herpes simplex and syphilis. All 107 patients who had TORCH laboratory results were above the age of 1 year, and all the patients had bilateral profound SNHL, hence it was difficult to differentiate between acquired and congenital infection of TORCH virus. Though the study was not ment for the diagnosis and corrective treatment of viral pathologies, our aim was to find out the incidence of CMV infection among TORCH virus infection in patients with profound sensorineural hearing loss.

Keywords: Cochlear implant, Congenital sensorineural hearing loss, TORCH.

Introduction
Among the many causes of hearing loss, viruses often are ignored. Viral infections, in particular cytomegalovirus (CMV), cause up to 40% of all congenitally acquired hearing loss. Many viruses can be the cause of congenital or acquired hearing loss. Typically, viruses cause sensorineural hearing loss (SNHL), however, a viral etiology has been proposed for otosclerosis also. Mechanisms involved in the induction of hearing loss by different viruses vary greatly, ranging from direct damage to inner ear structures, including hair cells and organ of Corti (as seen in some of the classically described causes of viral hearing loss such as measles), to induction of host immune-mediated damage. Infection with HIV can lead to conductive hearing loss (CHL) through bacterial and fungal infections, which become more frequent following the immunosuppression caused by that virus.

In The acronym TORCH (toxoplasma, rubella, cytomegalovirus, herpes simplex) was introduced in 1971 by Nahmis et al. Hearing loss caused by viruses can be mild or severe to profound, unilateral or bilateral.

Cytomegalovirus
CMV is a leading cause of congenital infections and long-term neuro developmental disabilities in children. The association between congenital CMV infection and SNHL has been known for over four decade, although the mechanism by which the virus causes hearing impairment in some children and not in others is not fully understood today. Approximately 40% of affected children are symptomatic and 10 % are without
clinically apparent disease. A recent review estimates that congenital CMV infection accounts for approximately 21% of all hearing loss at birth. The diagnosis of congenital CMV infection is difficult to establish after the first year of life because normal infants can become infected asymptomatically, shed virus in their urine, and show increased antibody titers. Fortunately, it is unusual for CMV infection acquired after birth to cause SNHL. The infection is detected by polymerase chain reaction (PCR) amplification of CMV DNA in urine, blood, saliva, and cerebrospinal fluid (CSF), or by the detection of CMV IgM antibodies in blood before 3 weeks of age, positive IgG results indicate past or recent CMV infection. These individuals may transmit CMV to susceptible individual through blood and tissue. When long-term sequelae become evident in previously asymptomatic infants, it is possible to make a retrospective diagnosis of congenital CMV infection by testing for the presence of CMV DNA in dried blood spot samples collected and stored from the neonatal screening period.

Rubella
The incidence of congenital rubella syndrome in developing countries has been reported to be 0.6-2.2 per 1000 live births. A strong association between rubella infection and hearing impairment is seen, infect infection with rubella virus has several teratogenic effects in pregnant women. CRS manifestations in surviving infants may include permanent structural defects like deafness, cataract and congenital heart disease. In our study, 2 patients were found to have CRS. The risk of vertical transmission from a non-immune mother with primary rubella infection in the first trimester of pregnancy is very high at 80-90%. Gestational age is considered to be critical factor in determining the degree of fetal damage following infection. Beyond the first 12 weeks of gestation, fetal organogenesis is nearly complete, and deafness may be the only consequence in the infected infant. Laboratory testing is useful in diagnosing congenital rubella infections; tests include the isolation of rubella virus from the urine of an infant during the first few weeks of life, isolation of the rubella virus from throat cultures, and documentation of increasing anti-rubella antibody titers during the first few months after birth. Antibodies in response to rubella are first detectable about 14 to 18 days after infection. Alternatively, a diagnosis can be made by detecting rubella-specific IgM in serum or oral fluid taken before 3 months of age, or by demonstrating persistent rubella IgG in serum taken between 6 and 12 months of age. Additionally, detection of rubella virus by PCR of samples from nasopharyngeal swabs, urine, CSF, and blood can also confirm infection up to the age of 1 year.

Toxoplasmosis
Congenital toxoplasmosis is caused by the transmission of the protozoan Toxoplasma gondii from the mother to the fetus. The main characteristics of congenital toxoplasmosis are: neurological and ophthalmological alterations, other symptoms of prematurity, intrauterine growth retardation, anemia, thrombocytopenia, increased abdominal volume, enlarged lymph nodes, jaundice, sensorineural deafness. Toxoplasma gondii has been associated with auditory pathway damage since the beginning of the 1950s, with evidence of calcium deposits (similar to calcifications found in the brains of children with congenital toxoplasmosis) in the spiral ligament and cochlea. Auditory deficit has been reported in about 20% of cases of congenital toxoplasmosis, especially in children not treated or treated for a very short period. IgG antibodies are produced by the body several weeks after the initial infection and provide long-term protection. Levels of IgG rise during the active infection, then stabilize as the Toxoplasma infection resolves and the parasite becomes inactive. Once a person has been exposed to T. gondii, that person will have some measurable amount of IgG antibody in their blood.
for the rest of their life. Infection with *T. gondii* is acquired through meat and meat products, from the environment through poor hygiene, and via contaminated surface water. Although human infection is usually asymptomatic and mild, fetal infection can result in serious disease. Most infants with congenital toxoplasmosis are asymptomatic initially, although 80-90% may develop eye and neurological diseases later in life. In infants, the presence of *T. gondii*-specific IgM or the persistence of IgG beyond 12 months of age is suggestive of congenital infection.

**Herpes Simplex Virus**

Neonatal herpes infection is a potentially devastating consequence of the common genital infection caused by human herpes simplex virus (HSV). Although previous reports have implicated HSV-2 as the primary cause of neonatal herpes, recent studies indicate that HSV-1 also plays a major role in causation. Primary maternal infection results in a higher incidence of neonatal herpes compared to reactivation disease in the mother. Intrauterine HSV infection during early pregnancy is rare; most neonatal HSV infections are parentally acquired via contact with infected lesions in the maternal genital tract. HSV DNA can be detected in the CSF by PCR, but although useful for diagnosing CNS and disseminated disease, it is present only in 70% of the cases. Serology has little value in the diagnosis of neonatal HSV infection due to high cross-reactivity between HSV-1 and HSV-2 and the late appearance of IgM antibodies.

**Materials and Methods**

All the 140 patients were asked for serological TORCH testing in the laboratory just to correlate the presence of specific antibodies, only 107 patients reported us back. All these patients with bilateral profound hearing loss since birth were enrolled for cochlear implant surgery in our institute. In our study we are concerned with TORCH virus specifically CMV infection in above patients.

**Observation**

Among all the 107 patients with congenital sensorineural hearing loss 58 (54.20%) were male while 49(45.79%) were female. 60 (56%) patients were found to have positive IgG antibodies for Cytomegalovirus. 42(39%) had rubella IgG positive levels in their serum. Table 1 showing the relative incidence of respective IgG serum level and male female ratio of the studied cases.

**Table 1**

|                | Toxoplasmosis | CMV | Rubella | HSV 2 | Total |
|----------------|---------------|-----|---------|-------|-------|
|                | IgG           | IgG | IgG     | IgG   |       |
| MALE           | 3             | 37  | 18      | 0     | 58    |
| FEMALE         | 2             | 23  | 24      | 0     | 49    |
| TOTAL          | 5             | 60  | 42      | 0     | 107   |

Among 107 patients none had positive IgM antibodies to corresponding antigen that suggest absence of any acute or recent virus infection. Table 2 shows the relative significance of presence of IgG and IgM antibodies and longevity of virus infection.

**Table 2**

| Results         | Interpretation                          |
|-----------------|-----------------------------------------|
| 1 IgG Positive  | Not previously infected, at risk of primary infection |
| IgM Negative    |                                         |
| 2 IgG positive  | Past CMV infection that is not recent    |
| IgM Negative    |                                         |
| 3 IgG positive  | Recent CMV infection                     |
| IgM positive    |                                         |

Among the patients, two were found to have (CRS congenital rubella syndrome); the classic triad of sensorinural deafness, cataract and congenital heart disease were seen. Cardiologist opinion were taken before any surgical procedure for this patients

**Discussion**

In our study, all patients with SNHL who were positive for virus infections assessed by TORCH were older than 1 year and none had confirmatory tests. TORCH is used mainly for screening pregnant women and infants who are small for gestational age (SGA) or who have microcephaly, unusual exanthemata, organomegaly, or thrombocytopenia. Children with established
bilateral profound SNHL will not benefit from TORCH investigations since there is currently no treatment that can reverse the profound hearing loss. However, if the screening had been performed early on, early management could prevent progression and stabilize hearing. The presence of IgG antibodies in the serum of these patients suggest previous infection by respective virus and all were above 1 year of age which suggests non placental transfer of antibodies. Serum obtained from all the patients were negative for IgM antibodies suggestive of absence of any acute infections.

CMV infection were suspected in most of the patients assessed by presence of serum IgG antibodies in around 60% of cases. This correlates with others studies also which briefs the similar incidence rate. The frequency of congenital CMV infection in children with bilateral SNHL varied from 3 to 36%. Children with bilateral hearing loss have speech developmental problems. Therefore retrospective diagnosis of congenital CMV infection is important to understand the etiology of SNHL. In Dublin, Cullen et al. reviewed laboratory results from TORCH screening from 1991 to 1995 and documented nine cases of CMV in a 5-year period, six of which had already been suspected. Shet et al. noted that infections acquired in utero or in the immediate post-natal period play a prominent role in prenatal and childhood morbidity. Their opinion is echoed by Holtmon et al., who evaluated the use of TORCH by pediatricians and pediatric trainees in a university pediatric department. They reexamined patient charts from 109 samples submitted to the Institute of Bacteriology from 1987 to 1991 for evidence suggestive of congenital infection, but found that the charts contained little information that could justify the ordering of a full TORCH panel. Overall the TORCH are one of the most common causes of hearing loss that leads to pediatric cochlear implantation (Smith et al) and CMV is the leading nongenetic cause of childhood SNHL. Hearing loss following viral infection is often sensorineural, although it may be mixed (CMV, measles) or conductive (measles). TORCH investigation in children with profound SNHL aged older than 1 year suggests significant association between incidence and occurrence rate of congenital defects, but not useful in early diagnosis and management of deafness.

Conclusion

In this review, we have discussed some of the more commonly known viral causes of infection that ultimately may be shown to be frequent causes of deafness. Some cause congenital hearing loss due to infection of the fetus in utero. Others cause hearing loss as a result of infection in childhood or adulthood. In our study CMV infection, congenital or acquired is the most common culprit causing profound sensorineural hearing loss. CMV is the leading nongenetic cause of childhood SNHL. Hearing loss following viral infection is often sensorineural, although it may be mixed (CMV, measles) or conductive (measles). TORCH investigation in children with profound SNHL aged older than 1 year suggests significant association between incidence and occurrence rate of congenital defects, but not useful in early diagnosis and management of deafness.

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