Review Article

Intrauterine infections as etiological factor for hearing Loss

B G Patil[1*], Alka B Patil[2]

{[1]Professor, Department of ENT} {[2]Prof & HOD, Department of OBGY} ACPM Medical College, Dhule, Maharashtra, INDIA.
Email: alkabpatil@rediffmail.com

Abstract

Hearing is an essential sensory sense of an individual for development of speech. Deafness not is considered as a social stigma. When sensoryneural hearing loss is present at birth,it is either genetic problem or due to intrauterine or perinatal causes. Intrauterine infections causing hearing loss are grouped as viral, bacterial or parasitic. In this review article, we evaluate etiological factors for hearing loss due to intrauterine infections: Cytomegalus, Rubella, Lymphocytic Choriomeningitis Virus, HSV1, HSV2, HIV, Toxoplasmosis, syphilis. Interventions available for their prevention and treatment are explored.

Key Word: Sensory neural hearing loss, choriomeningitis Virus, HSV1, HSV2, Cytomegalovirus, Rubella, Lymphocy tic Choriomeningitis Virus, HIV, Toxoplasmosis, syphilis.

[*]**Address for Correspondence:**
Dr. B G Patil, Professor, Department of ENT, ACPM Medical College, Dhule, Maharashtra, INDIA.
Email: alkabpatil@rediffmail.com
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INTRODUCTION

Hearing is an essential sensory sense of an individual for development of speech which is crucial for verbal communication and personality development. Hearing impairment is one of the most frequent sensory deficits in human beings. It is the second most common form of disability after loco motor disability in our country.[1] Hearing loss is relatively common in human population and is caused by multiple etiological factors. Profound hearing loss is estimated to occur in one in 1000 live births. The prevalence of moderate to severe hearing impairment in India is about 6.3% implying about 630,567,000 hearing impaired in India alone. Some congenital SNHL which is acquired early in life,is unfortunately bilateral and profound. If such SNHL is not recognized at an early age, the child will not be able to develop speech and language. When SNHL is present at birth, it is either a genetic problem or due to intrauterine or perinatal causes. Intrauterine infections causing hearing loss are grouped as viral, bacterial or parasitic.[2] In this review article, we evaluate viral infections as etiological factors in hearing loss. We explore Syphillis, Toxoplasmosis causing hearing loss. We highlight chorioamnionitis, a lifethreatening obstetric complication causing hearing infant. Extensive discussion regarding treatment of these infections is beyond the scope of this article.

Cytomegalovirus

CMV is an extremely common viral infection with nearly 100% prevalence. Like all herpesviruses, CMV is a double-stranded enveloped DNA virus that can remain latent in the body long after primary infection. CMV can reactivate and cause disease in immunocompromised hosts. CMV is typically acquired early in life and may be acquired in utero. CMV transmission to fetuses can occur during primary maternal infection accounting for 40–50% of cases of congenital CMV or reactivation during pregnancy 1% of cases of congenital CMV. Congenitally acquired CMV is included as one of the TORCHS, an acronym for frequently occurring infectious teratogens toxoplasmosis, rubella, CMV, herpes simplex, and syphilis, respectively. All of the TORCHS infections can cause similar signs before and after birth as well as

similar birth defects. These include reduced intrauterine growth, microcephaly, seizures, mental retardation, visual defects, and cerebral palsy. Overall, the TORCHS are one of the most common causes of hearing loss that lead to pediatric cochlear implantation. Maternal infection with CMV earlier in pregnancy increases the risk of symptomatic infection. Only 5% to 10% of infected neonates will show signs of CMV infection at birth. Among these symptomatic infants, mortality is high 5%, and infants who survive often have permanent neurological defects such as SNHL, visual deficits, and seizures. CMV is the leading nongenetic cause of childhood SNHL. Hearing loss can occur in both symptomatic and asymptomatically infected children. Delayed manifestations of congenital CMV infection, particularly SNHL, can manifest months or years after birth. Initial hearing screens will miss the majority of cases of SNHL in CMV-infected children. The average age of diagnosis of hearing impairment in congenitally infected children is 27 to 33 months. Hearing loss may be diagnosed many years later, and thus CMV may be the cause underlying many cases of idiopathic SNHL in children;. Of children born with symptomatic CMV infection, 14% will develop hearing loss and 5% will have severe, bilateral SNHL. The etiology of SNHL resulting from CMV infection is not fully understood. Temporal bone studies demonstrate inflammation and edema of the cochlea and spiral ganglion, and viral antigens in the spiral ganglion, organ of Corti, scala media, and Reissner's membrane. Recent research in a guinea pig model system demonstrates that CMV expresses proteins that trigger an immune response that leads to hearing loss and inflammation within the cochlea. This theory of pathogenesis may not fully explain progressive or later onset hearing losses seen in patients following CMV infection in utero.

The presentation, severity, progression, and audiographic pattern of SNHL resulting from congenital CMV infection are highly variable;. Following identification of SNHL in children with CMV, continued audiographic monitoring is necessary due to frequent progression. Hearing loss in children who were initially symptomatic tends to be bilateral, more severe, and more likely to progress. Ganciclovir is the treatment for both early and delayed SNHL resulting from congenital CMV infection. Ganciclovir prevents SNHL progression and sometimes can improve hearing status. This medication must be administered intravenously and can be associated with neutropenia. Other options include valganciclovir a prodrug of ganciclovir that can be given orally, cidofovir, and foscarnet. Studies are currently underway testing the efficacy and duration of treatment of infected neonates with valganciclovir. Ganciclovir is teratogenic in animal studies and so cannot be used to treat pregnant women with active CMV infection. Other treatment modalities also exist. In vitro and animal studies support the use of CMV hyperimmune globulin during pregnancy. SNHL that does not respond to antiviral medications can be treated with hearing aids or cochlear implantation depending on hearing severity. Cochlear implantation can significantly improve hearing loss due to CMV infection; however, the extent of improvement in speech and language skills following cochlear implantation may not be as great as in non-CMV-infected children with severe to profound hearing loss. Despite multiple attempts at vaccine development, there is not currently an effective CMV vaccine. Prevention of primary infection in previously uninfected pregnant women is therefore the mainstay of limiting congenital CMV infection. Pregnant women are encouraged to frequently wash their hands and to avoid contact with saliva or urine of children younger than 6 years, particularly if they are enrolled in daycare.[3] Few, if any, pregnant women are routinely screened for CMV infections during pregnancy. Questions surrounding the appropriateness of serologic screening for CMV during pregnancy are important because over 90% of primary maternal CMV infections during pregnancy are asymptomatic and may remain asymptomatic in the fetus.[4]

Rubella

Rubella, also known as the German measles, is a member of the *Togaviridae* family of viruses. The genome of this virus is a single-stranded RNA and is enclosed in an icosahedral nonenveloped capsid. Rubella is most commonly transmitted via contaminated upper respiratory secretions during coughing, sneezing, and talking. If the virus is acquired during pregnancy it is a potent teratogen and one of the TORCHS infections. Congenital rubella syndrome manifests as hearing loss, congenital cataracts, microcephaly, mental retardation, thrombocytopenia, cardiac anomalies, and a characteristic rash the so-called blueberry muffin spots.3

Rubella is one of the most teratogenic agents known. As the duration of pregnancy increases, fetal infections are less likely to cause congenital malformations. Thus clinical manifestations of congenital rubella correlate with the timing of maternal infection and fetal organ development.[5] SNHL is the most common sequela of congenital rubella infection 58% and is most often seen when maternal rubella infection occurs within the first 16weeks of pregnancy. Vestibular function is spared.[3] Rubella virus has a low destructive potential for rapidly growing cells. Vascular insufficiency is the cause in congenital defects associated with Rubella. Chromosomal break ups, reduced cellular multiplication time and

increased production of protein inhibitor that causes mitotic arrest of certain cell types are the ways in which Rubella virus acts. Hearing loss typically manifests in the first 6 to 12 months of life, although it can present at birth. Audiograms often show a flat, uniform mild to severe SNHL, but isolated high-frequency hearing loss has been reported.While the mechanism of rubella-induced hearing loss has not been fully explained, the virus causes direct cochlear damage and cell death in the organ of Corti and stria vascularis. Alterations in the composition of endolymph due to strial damage have also been described.Depending on the severity of hearing loss,treatment options include the use of hearing aids and cochlear implantation.[3] Most of the previous studies on the etiological factors for deafness indicated maternal rubella as a high risk prenatal factor causing congenital deafness. Studies carried out by Peckham *et al.* in children with sensorineural deafness, observed 24% of the cases with congenital Rubella syndrome. Immunological studies carried out in Poland in seropositive women for rubella during first trimester of pregnancy showed the presence of IgG and IgM antibodies in them and in their fetus and hearing loss was confirmed in 50% of the children born to them.[198 hearing-impaired children and 200 controls were tested for rubella antibody IgG using ELISA in Bangladesh. The results showed 74% subjects and 18% controls with rubella antibody suggesting a high prevalence of rubella infection in Bangladesh and indicating implementation of vaccination against rubella infection. Studies on 75 children with deafness due to embryopathy from maternal rubella showed 15 cases with an interauricular auditory functional asymmetry, which is one of the elements of etiological diagnosis and which enables better adaptation of a hearing aid for rubella-induced deafness. In the study conducted by Dr M VV Reddy and Hema Bindu, etiological factors were studied in 1076 hearing impaired children below 14 years of age. The results of their study indicated only 1.57% children with rubella-induced deafness. This showed that rubella is not a high risk factor for congenital deafness in developing countries. The probable reason behind this could be the appropriate vaccination of the mothers with the rubella antigen during the pregnancy. Recent reports indicate that deafness due to intrauterine rubella infection was less compared to congenital hearing loss occurring due to CMV infections and alcohol fetopathia.[7] With the incidence of Rubella vaccine, there has been a progressive and significant reduction in the incidence of congenital Rubella. Rubella vaccine should be avoided one month before or during pregnancy, as it contains live virus.[8] In areas without routine rubella vaccination, congenital rubella remains a common cause of severe to profound bilateral SNHL. In a recent Brazilian study, congenital rubella was thought to be the cause of hearing loss in 32% of patients with deafness. Following the institution of a "school girl" vaccination program in Western Australia, the rate of congenital rubella syndrome dropped to 0% in vaccinated mothers.[3]

Lymphocytic Choriomeningitis Virus

Lymphocytic choriomeningitis virus LCMV is a single-stranded enveloped RNA virus. LCMV is a member of the *Arenaviridae* family and has been identified as an emerging teratogen Rodents, including the common house mouse, are the natural hosts and serve as reservoirs of LCMV. Infection is transmitted to humans through contact with rodent urine, feces, or saliva, and occurs more commonly in winter months when mice seek shelter indoors.The virus is not typically spread between humans; however, there have been cases of transmission via organ transplantation. In immunocompetent adults, LCMV infection is typically either asymptomatic or associated with upper respiratory tract infection symptoms fever, headache, nausea, and vomiting. Rarely, complications such as aseptic meningitis and meningoencephalitis occur. LCMV infection in pregnancy greatly increases the risk of spontaneous abortion. LCMV infection can also be teratogenic, especially if the virus is contracted during the first or second trimester, and is associated with microcephaly, hydrocephalus, ventriculomegaly, pachygyra, cerebellar hypoplasia, chorioretinitis, periventricular calcification, and hearing loss. In contrast to congenital CMV or rubella, visual impairment and microcephaly are much more common than hearing loss in congenital LCMV infection. LCMV can also be distinguished from these other congenital viral causes of hearing loss by the lack of hepatosplenomegaly.Enzyme-linked immunosorbent assay ELISA for LCMV IgG and IgM antibodies can establish the diagnosis of congenital LCMV infection. Hearing loss in these patients can vary in severity between ears, and ranges from severe to profound SNHL. Ribavirin, a nucleoside inhibitor used to stop viral RNA synthesis and capping, has been used to treat LCMV infection in adults. Ribavirin is a teratogen in many animal models and should not be used to treat pregnant. Treatment of hearing loss in affected children with hearing aids and other assistive listening devices is indicated when appropriate. Treatment of severe to profound SNHL in children with congenital LCMV may be limited in patients in whom involvement of the vestibulocochlear nerve is the cause of hearing loss; however, because severe visual impairment is seen in all children with congenital LCMV infection, it should be attempted.[3]

Human Immunodeficiency Virus

HIV is the retrovirus that causes AIDS. Common symptoms within the temporal bone include hearing loss, tinnitus, chronic otitis media, facial nerve palsy, and malignancies. Infants can develop hearing loss following either infection or exposure in utero without infection. Hearing loss associated with HIV infection can be unilateral or bilateral, progressive or sudden, and conductive, sensorineural, or mixed. Hearing loss in HIV-infected patients can be caused by a number of factors, including the direct effects of HIV, increased susceptibility to opportunistic infections in the middle ear and brain, and treatment with potentially ototoxic medications Khoza-Shangase *et al.*., 2011. CHL often results from recurrent otitis media, otitis externa, acquired aural atresia, cholesteatoma, formation of aural polyps, or malignancy. Rarely, SNHL may be the only presenting symptom of HIV infection HIV has been detected in auditory and vestibular hair cells, strial cells, and along the tectorial membrane. Use of antiretroviral cocktails reduces HIV transmission from infected mothers to fetuses and breastfeeding children from 25% to 48% to 1% to 2%. Hearing aids can be used in the treatment of HIV-infected patients with mild to moderate SNHL. For patients with severe to profound SNHL, cochlear implantation can be successful.[3]

HSV Types 1 and 2 HSV types 1 and 2 have been implicated as causes of hearing loss. Both are encapsulated, double-stranded DNA viruses of the herpesvirus family. Infection follows contact of mucous membranes or broken skin surfaces with infected fluids from herpes sores or with other body fluids of patients with herpes. The viruses can latently infect nerve cells innervating the initially infected tissue. Congenital herpes infection typically arises due to exposure to HSV1 or HSV2 during delivery. Neonatal infection is more frequent from women who develop infection late during pregnancy or who have active herpetic lesions in the birth canal. However, 30% of pregnant women without prior history of HSV2 may be serologically positive and have asymptomatic viral shedding, which can lead to neonatal infection. Many 62% of HSV2-infected mothers are HSV1 positive as well. Neonatal HSV1 infection occurs in 1/2,000 to 1/8,000 and HSV2 in 5.9/100,000 live births. Sequelae of neonatal infection range from eye and mucous membrane involvement to disseminated disease, encephalitis, hearing loss, mental retardation, microcephaly, and death. Many infected infants will not have a vesicular rash and so may not be tested for HSV infection. HSV1 infection is much more frequently associated with encephalitis and hearing loss following infection in neonates compared with HSV2 However, hearing loss following HSV1 infection is relatively rare and typically associated with concomitant severe neurological complications. Hearing loss following neonatal infection can be bilateral or unilateral severe to profound SNHL. Following infection with HSV1 or HSV2, fibrosis of the scala tympani and vestibule, loss of outer hair cells, and atrophy of the stria vascularis and tectorial membrane were found in animals. Viral antigens were located throughout the cochlea, and viral capsids were found within cochlear nerve fibers, including both afferent and efferent nerve endings. There currently are no approved vaccines for HSV1 or HSV2. Prevention of neonatal HSV infection can be achieved by preventing transmission of herpes simplex from infected mothers to their infants during delivery. Women with primary HSV1 or HSV2 contracted during pregnancy should be treated with 400 mg of oral acyclovir three times a day TID for 7 to 10 days, regardless of the timing of the occurrence. In addition, the American College of Obstetricians and Gynecologists recommends herpes suppressive therapy for these women from 36 weeks gestation to delivery. Similarly, women with recurrent herpes should receive herpes suppressive therapy from 36 weeks until delivery. Cesarean delivery is recommended for women with active herpes lesions at the time of delivery Treatment of hearing loss associated with HSV1 or HSV2 infections includes treatment with antiherpetic agents and steroids. Hearing loss that does not recover following treatment with steroids and antiherpetic agents can be remediated with hearing aids or cochlear implantation, depending on the severity of loss.[3]

Toxoplasmosis

Toxoplasma gondii is a ubiquitous parasite whose definitive hosts are members of the Felidae cat family. Intermediate hosts include almost all warm-blooded mammals and birds, including humans, who accumulate infectious, quiescent stages bradyzoites of the parasite in their tissues, particularly in skeletal muscle and the brain. Toxoplasma gondii is of particular concern in humans because of the potential for transmitting the disease to the unborn fetus if the mother is infected for the first time during pregnancyPatients with a history of recent miscarriage, ocular infection, jaundice, hepatosplenomegaly, and cirrhosis of the liver may be referred into a testing protocol termed “TORCH” T. gondii, other [if done, e.g., syphilis, varicella zoster virus, human immunodeficiency virus, and parvovirus B19, rubella, cytomegalovirus [CMV], and herpes simplex viruses [HSVs], to rule out infections with similar The TORCH infections can cause serious illness or death to the fetus or neonate, so TORCH testing is important to protect the health of neonates that may have been exposed

to one or more TORCH pathogens in utero. Congenital CMV has similar manifestations to toxoplasmosis and rubella that include sensorineural hearing loss, mental retardation, and retinochoroiditis. Pregnant women should take appropriate precautions to protect themselves against infection In the absence of universal screening, primary prevention of congenital toxoplasmosis through heightened maternal education efforts can be an effective strategy to prevent transmission to the fetus. The high percentage of at-risk females in their childbearing years 65% suggests that pregnant women should receive counseling during their antenatal visits on how to prevent T. gondii infection. Population-based studies or universal screening of newborns over a specified time period could elucidate the true burden of congenital toxoplasmosis and suggest priorities for public health action.[9]

Syphillis

Congenital syphilis is still a cause of perinatal morbidity and mortality.. Clinical manifestations of congenital syphilis are influenced by gestational age, stage of maternal syphilis, maternal treatment, and immunological response of the fetus. Diagnosis of maternal infection is based on clinical findings, serological tests, and direct identification of treponemes in clinical specimens. Spirochetes can cross the placenta and infect the fetus from about 14 weeks' gestation, and the risk of fetal infection increases with gestational age.Clinical manifestations of congenital syphilis are influenced by gestational age, stage of maternal syphilis, maternal treatment, and immunological response of the fetus. Eight nerve deafness occurs in 3% of cases and is secondary to luetic involvement of the temporal bone.[10] In early congenital syphilis birth to 3 years, hearing loss is rapid, bilateral, profound, symmetrical. Prognosis is poor in early congenital syphilis.[11] Syphilis infection during pregnancy still represents a worldwide public health problem. The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics recommend prenatal syphilis screening at the first prenatal visit and again at 32–36 weeks, if the woman is at risk for syphilis]. CDC recommends that all women should be screened serologically for syphilis at the first prenatal visit and, for patients at high risk, during the third trimester and at delivery. Preconception serological tests for syphilis could represent the key to reduce the incidence of CS. Moreover, preconception counseling could play an important role, evaluating the woman and her partner for exposure to sexually transmitted diseases, identifying high-risk behaviors, and providing health promotion messages and education.[10]

Chorioamnionitis

Clinical chorioamnionitis, characterised by maternal fever, leukocytosis, tachycardia, uterine tenderness, and preterm rupture of membranes, is less common than subclinical/histologic chorioamnionitis, which is asymptomatic and defined by inflammation of the chorion, amnion, and placenta. The incidence of intrauterine inflammation is inversely related to gestational age, such that it is implicated in the majority of extremely preterm births and 16% of preterm births at 34 weeks. Microbiological studies indicate that intrauterine inflammation is associated with approximately 25–40% of all preterm births. The majority of fetuses exposed to chorioamnionitis develop a systemic inflammatory response known as the fetal inflammatory response syndrome FIRS. This is due to the fetus being in direct contact with infected amniotic fluid and/or inflammatory cell transfer from the uteroplacental circulation. The fetal inflammatory response syndrome FIRS is defined by increased systemic inflammatory cytokine concentrations, funisitis, and fetal vasculitis. FIRS can itself be categorised as clinical or subclinical. Clinical FIRS is defined by a fetal plasma [interleukin-6] >11 pg/mL, whilst subclinical FIRS is defined histologically by funisitis and fetal vasculitis.Histological chorioamnionitis is also associated with an increased incidence of speech delay and hearing loss at 18 months of corrected age in infants born very preterm. Available clinical, epidemiological, and experimental data indicate that chorioamnionitis plays a significant role in predisposing the preterm infant to multiple organ disease. Further investigation is required to improve our understanding of the mechanisms underlying the changes in development and function of the preterm cardiorespiratory, central nervous, visual,auditory and renal systems. Improved antenatal screening for chorioamnionitis and identification of effective treatment strategies for preterm infants exposed to intrauterine inflammation will likely provide a better prognosis for infants at risk of multiple organ disease as a result of exposure to inflammation before birth.[12]

DISCUSSION

Deafness not be considered as a social stigma and it needs to be treated at par with other disabilities / physical challenge. Apart from Government, the physicians have got a moral as well as social duty to dedicate ourselves and work for prevention and controlcure of deafness. There is need to identify the possible cause of deafness as well as measures which can be taken to control / prevent/minimize or eradicate this physical deficiency to the extent clinically feasible. Deficiency of iron Vit D, folic acid affects the baby leading to poor physical and mental development along

with overall age retardation. Nutritional deficiency may aggravate the prenatal and postnatal infections.

Deafness and hearing is the second commonest form of disability in India. Early and accurate identification with timely intervention is a must to decrease deafness from our society.These interventions will translate into miles of travel to reach destination. A number of viral infections can cause hearing loss. A baseline knowledge of these viruses is critical in the recognition of their involvement in hearing loss in affected patients. Hearing health care providers may encounter frequent questions from parents of children with hearing loss, questioning whether specific viral infections or vaccinations for these viruses have caused their child's hearing loss. In this review, we have discussed some of the more commonly known viral causes of hearing loss as well as a few emerging viral infections that ultimately may be shown to be frequent causes of deafness. Some cause congenital hearing loss due to infection of the fetus in utero Hearing loss following viral infection is often sensorineural, although it may be mixed CMV, measles or conductive measles. Auditory system damage is typically intracochlear; however, some viruses can affect the auditory brainstem as well. Mechanisms of injury to the peripheral auditory system can include direct viral damage to the organ of Corti, stria vascularis, or spiral ganglion. Hearing loss due to CMV infection can be treated medically with stabilization or improvement in hearing threshold. Rehabilitation of hearing loss due to other viruses typically involves hearing aids, with cochlear implantation for patients with severe to profound hearing loss. Recent developments that make either universal or limited serologic screening for CMV during pregnancy potentially attractive. The developments include an understanding of the pathogenesis of CMV infections, a knowledge of high-risk women, the availability of accurate methods for the serologic diagnosis of a primary CMV infection using either single or serial blood samples, accurate methods for the diagnosis of fetal infection via amniotic fluid, sensitive fetal and placental indicators for neonatal outcomes, and the availability of potentially effective interventions. A child with congenital SNHL is likely to develop psychological problems. In most Western countries universal hearing screening is carried out for all newborns. This helps to identify hearing loss during infancy itself. Early detection of hearing loss is important because sound amplification with devices such as hearing aids, cochler implants and other hearing devices /implants together with speech therapy should be started as early as possible for cochlear implantation and also for adequate speech and language development, either with aid of cochlear implant or hearing aid.

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