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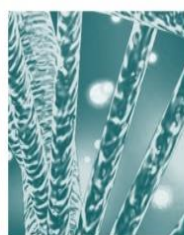
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Congenital Cytomegalovirus Infection as a Cause of Paediatric Sensorineural Hearing Loss

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ABSTRACT

Objective: To determine the association between sensorineural hearing loss (SNHL) and congenital cytomegalovirus (CMV) infection diagnosis with pediatric patients.

Methods: This cross-sectional investigation encompassed a cohort of 60 children (ages 1–16 years) diagnosed with sensorineural hearing loss (SNHL), who were recruited from the Audiology Department of Children's Hospital Lahore during the period from September 2017 to February 2018, subsequent to receiving Institutional Review Board (IRB) authorization. The severity of SNHL was categorized utilizing pure-tone audiometry (according to AAO criteria), while the diagnosis of CMV infection was established through serum antibody assessment employing the chemiluminescence method (Access 2 system). Demographic and clinical information were gathered via a structured questionnaire after obtaining informed consent. Automated serological testing estimated CMV IgG and IgM antibodies in blood samples.

Results: Out of 60 cases, (56.67%) patients were females and (43.33%) patients were male while 44(73.33%) patients observed with CMV IgG reactive and only 16(26.67%) patients observed with CMV IgG nonreactive. and out of 60 cases 14(23.3%) patients observed with CMV IgM reactive and 46(76.67%)CMV IgM nonreactive. Predictors of paediatric sensorineural hearing loss identified by logistic regression were male (OR:2.12, CI 95%:0.205-5.58; P value = 0.93), age (OR:1.00, CI 95%:0.954-1.05; P value = 0.961), weight (OR:3.82, CI 95%:0.795-18.3; P-value 0.094), positive reaction of CMV IgG (OR:1.88, CI 95%: 0.43-1.78; P value = 0.45) and positive reaction of CMV IgM level (OR:1.89, CI 95%: 0.92-3.98; P value = 0.092).

Conclusion: In conclusion, congenital CMV infection plays a major role as a cause of bilateral and unilateral SNHL in children that was hospitalized in Children Hospital Lahore.

Keywords: Cytomegalo Virus, immunoglobulin G, immunoglobulin M. Pure tone audiometry, Enzyme linked immune sorbent Assay

1. INTRODUCTION

Sensorineural hearing loss (SNHL) is a substantial health concern in the pediatric population, impacting communication, social development, and academic performance¹. Among the various etiologies of SNHL, congenital cytomegalovirus (cCMV) infection stands out as a leading, yet often under-recognized, cause².

Cytomegalovirus (CMV) is a ubiquitous herpesvirus, with an occurrence predictable to reach as 60-90% in adults globally. While CMV infection is typically asymptomatic in immunocompetent individuals, its implications during pregnancy are profound³. Congenital CMV infection occurs when a pregnant woman transmits the virus to her fetus. This can happen through primary infection, reactivation of a latent infection, or reinfection with a different CMV strain during pregnancy^{4,5}.

The incidence of cCMV infection varies geographically but is estimated to affect approximately 0.5-2% of all live births⁶. Although the majority of infants with cCMV are asymptomatic at birth, about 10-15% of these congenitally infected children will develop persistent consequences with SNHL being the extremewidespread.^{6,7}

SNHL caused by cCMV can vary from slight to extensive and may be unilateral or bilateral. The hearing loss can either be present at birth or develop later, sometimes happening years after birth. This variability makes early identification and intervention challenging but critical for optimizing language and cognitive outcomes in affected children.¹

The pathogenesis of cCMV-induced SNHL involves viral replication and subsequent inflammation within the cochlea, leading to damage of the inner ear structures. Additionally, the virus can disrupt the development of the auditory pathway, further contributing to hearing impairment^{1,8}.

Despite advances in diagnostic techniques, cCMV remains underdiagnosed. Routine newborn hearing screenings, while essential, do not differentiate the cause of hearing loss, necessitating further investigation in cases of unexplained SNHL⁹. Early identification of cCMV can facilitate timely antiviral treatment, potentially mitigating the severity of hearing loss and other developmental impairments^{9,10}. This introduction aims to highlight the critical role of cCMV in pediatric SNHL, emphasizing the need for increased awareness, early diagnosis, and intervention strategies to improve outcomes for affected children.

This study aims to establish guidelines for recognizing congenital cytomegalovirus (cCMV) as a cause of sensorineural hearing loss (SNHL) in children and to contribute to therapeutic interventions. It underscores the importance of regular follow-ups due to the disease's progressive nature and highlights the need for more epidemiological data on cCMV. Early identification is critical as delayed detection can impair language, cognitive, and psychosocial development, and neonatal screening alone may miss later-developing hearing loss.

2. METHODOLOGY

This observational cross sectional based study of 60 consecutive children diagnosis with sensorineural hearing loss (SNHL) disease, age ≥ 1 to 16 years were selected after the approval from the children's hospital Institutional Review Board, from audiology department of children's hospital Lahore over a period of six month from September 2017 to February 2018. Patients with other causes or types of hearing loss were excluded from the study.

Sensorineural hearing loss (SNHL) was defined as a type of hearing loss resulting from damage to the inner ear (cochlea) or the auditory nerve pathways and measured using pure-tone audiometry (AAO criteria), with the following cut-off values:¹¹

Mild SNHL: 26-40 dB HL

Moderate SNHL: 41-55 dB HL

Moderately Severe SNHL: 56-70 dB HL

Severe SNHL: 71-90 dB HL

Profound SNHL: > 90 dB HL

while CMV virus was diagnosed by serum blood test based on antibody levels measured using the chemiluminescence technique on the Access 2 system, with the following cut-off values:¹²

CMV IgG: Non-reactive: < 11.0 AU/ml

Reactive: > 15.0 AU/ml

CMV IgM: Non-reactive: < 0.80 AU/ml

Reactive: > 1.0 AU/ml

Patients were included after taking consent form while questionnaire was used for data collection, which will include parameters of study i.e. demographical (age, gender, weight defined by using BMI as weight (kg)/height (m²) with a cut of value BMI z-score is <-2 considered as underweight, head circumference with a cut of value < 3rd percentile)¹³ and clinical characteristics regarding procedure. Firstly, the samples were centrifuged at 1500 RPM for 2-3 minutes to separate the serum. The serum samples were then placed into the rack sequentially until the rack was complete. Next, the test requests were ordered, and the tests for CMV IgG and IgM were selected. Before running the samples on the Access 2, which is fully automated, all supplies such as substrate, buffer, reagent, and reaction vessels (RVs) were checked. After ensuring all supplies were in place, the RUN button was pressed to initiate the sample processing. After a period, the results were generated and either noted or printed.

The data were entered and analyzed using SPSS 21.0. Descriptive statistics, including central tendency and dispersion, were reported for quantitative variables, while frequencies and percentages were provided for qualitative variables. The Shapiro-Wilk test was utilized to assess data normality. To examine the association between congenital cytomegalovirus infection and pediatric

sensorineural hearing loss, Pearson Chi-Square and Fisher Exact tests (for cell frequencies less than 5) were used. For quantitative variables, two independent sample t-tests were applied to explore this association. Logistic regression analysis was employed to assess the influence on pediatric sensorineural hearing loss. A significance level of 5% was applied to all two-tailed tests.

3. RESULTS

A high percentage (73.33%) of individuals tested positive (reactive) for CMV IgG antibodies. This indicates that these individuals have been exposed to CMV at some point in the past and have developed immunity. CMV IgG remains in the body for life, so a positive result usually signifies a past infection. A smaller percentage (23.33%) of individuals tested positive (reactive) for CMV IgM antibodies. IgM antibodies are typically produced by the body in the early stages of an infection. A positive (reactive) CMV IgM result usually suggests a recent or current CMV infection, though false positives can occur, and additional testing may be required for confirmation as shown in table-1:

The data indicates that CMV IgG reactivity is more common in individuals with mild to moderate and moderate to severe SNHL. A p-value of 0.017 indicates that there is a statistically significant association between past CMV IgG reactivity and the degree of SNHL. In contrast, CMV IgM reactivity is less common in individuals with more severe forms of SNHL, implying that recent or current CMV infection is less associated with severe SNHL. A p-value of 0.0105 indicates a statistically significant association between CMV IgM reactivity and the degree of SNHL as shown in table-2:

Binary logistic regression results indicate that who were male (OR:2.12, CI 95%:0.205-5.58; P value = 0.93), Age (OR:1.00, CI 95%:0.954-1.05; P value = 0.961), weight (OR:3.82, CI 95%:0.795-18.3; P-value 0.094), positive reaction of CMV IgG (OR:1.88, CI 95%: 0.43-

1.78; P value = 0.45) and positive reaction of CMV IgM (OR:1.89, CI 95%: 0.92-3.98; P value = 0.092) were significantly associated with the development of paediatric sensorineural hearing loss.

Nagelkerke R² value in this study analysis was (0.309) which signify that factor in this study contributing only (30.9%) to PSHL. Other factor contributing was not included in the study. The classification table shows that the overall predictive accuracy is 80.4% as shown in table-3.

Table-I: Descriptive and inferential statistics of the congenital cytomegalovirus infection patients

Gender n (%)	Male	26/60(43.33%)
	Female	34/60(56.67%)
Age in month		36±20
CMV IgG n (%)	Reactive	44(73.33%)
	Non-reactive	16(26.67%)
CMV IgM n (%)	Reactive	14(23.33%)
	Non-reactive	46(76.67%)
SNHL n (%)	unilateral	12(20%)
	bilateral	

Table-II: Association of the congenital cytomegalovirus infection with paediatric sensorineural hearing loss

Charecteristics		SNHL			P-value
		Mild to moderate	Moderate to severe	Severe to profound	
CM V IgG	Reactive	18/19	20/29	6/12	0.017
	Non-reactive	1/19	9/29	6/12	
CM V IgM	Reactive	9/19	4/29	1/12	0.0105
	Non-reactive	10/19	25/29	11/12	

Table-III: Regression analysis of the Paediatric Sensorineural Hearing Loss with predictors.

Charecteristics	B	Wald	Sig.	Exp(B)
Age	0.001	0.002	0.961	1.001
Male	0.753	1.141	0.286	2.124
Female	-0.024	0.567	0.451	0.976
Under-weight	1.34	2.799	0.094	3.819
Head circumference	-0.028	0.083	0.774	0.973
CMV IgG	0.65	0.45	0.32	1.88

CMV IgM	0.64	2.847	0.092	1.896
Constant	-14.135	1.356	0.244	0

4. DISCUSSION

Cytomegalovirus (CMV) is a widespread herpesvirus transmitted through close personal contact and establishes lifelong latency in monocytes and granulocytes. Infants can acquire CMV infection through congenital, intrapartum, or postnatal routes¹⁴. Approximately 13.5% of asymptomatic neonates may later experience neurodevelopmental issues, with hearing loss being a common manifestation. Hearing loss is frequently observed in cases of CMV infection.¹

Sensorineural hearing loss resulting from congenital infection is often progressive and can be either unilateral or bilateral¹⁶. It may not be apparent at birth but can become clinically evident later in childhood. Congenital CMV infection is responsible for approximately 21% of hearing loss at birth and 25% of hearing loss by age 4, highlighting the need for regular hearing assessments and early intervention for affected children¹⁻⁵. The link between congenital CMV infection and sensorineural hearing loss has been recognized for over forty years. Children with congenital CMV infection often experience significant developmental challenges: 34.0% have speech and language delays, 12.8% show motor delays, 11.3% face balance issues, and 4.3% encounter cognitive delays¹⁷. These findings emphasize the need for thorough interdisciplinary evaluations and vestibular assessments. In this study, hearing loss was observed in patients up to 16 years old at Children's Hospital Lahore who tested positive for CMV serology (IgG and IgM).

The current study suggests that CMV infection is a more prominent factor in the development of sensorineural hearing loss (SNHL) than previously indicated. Among 60 SNHL cases, 44 (73.33%) tested positive for CMV IgG, and 14 (23.33%) tested positive for CMV IgM. Additionally, there was a statistically significant association between past CMV IgG reactivity and the severity of SNHL shows $P\text{-value} < 0.05$. These results align with some studies but differ from others, such as those by Goderis¹⁹, and Grosse²⁰, which reported incidences of hearing loss ranging from 12% to 20%.

A study conducted by Furutate S et al²¹ found that 9.0% (12 out of 134) of children with sensorineural hearing loss had congenital CMV infection as the cause. In that study which shows the relationship concerning CMV and hearing loss supported over study which also shows CMV is a leading cause of hearing loss in offspring. Another study conducted by Barbie et al²² concluded that the congenital CMV infection is a crucial element of SMHL, but the exact magnitude is uncertain. Published reports suggest that congenital CMV accounts for 33% to 44% of SNHL and children as the basis for their estimate that congenital CMV infection. In a study, 10 to 12% of cases of mild to severe sensorineural hearing loss (SNHL) were found to be associated with congenital cytomegalovirus (CMV) infection. Another study by Foulon I et al¹⁸ observed that hearing loss was more common in cases of symptomatic infection at birth, with an incidence of 23.1% ($P = .017$). A recent systematic review by Vos B et al²³ reported that the manifestation of sensorineural hearing loss (SNHL) at birth exceeds 33% in infants with symptomatic

CMV infection, while it is less than 15% in those with asymptomatic infections.

The current study reported contradictory results, suggesting that environmental or genetic factors might be involved. It is proposed that host-derived inflammatory responses, rather than direct virus-mediated cytopathology, may be responsible for hearing impairment, which could explain the unpredictable nature of cochlea-vestibular damage.

Another study by Peckham CS et al²⁴ suggested that each year in England and Wales, about 108 children are born with congenital CMV infection and bilateral sensorineural hearing loss, representing 12% of all cases of congenital sensorineural hearing loss. CMV pervasiveness in the urine of children with sensorineural hearing loss and no family history of deafness is nearly twice as high (13%) associated to other children with hearing loss or normal hearing (7%).

Yamamoto AY et al²⁵ examined that sensorineural hearing loss (SNHL) is more regularly observed in symptomatic CMV infection, with an incidence of 9.8%. These studies showed differing results, partly due to the lack of information about the rate of congenital CMV (cCMV) infection in the general population. Additionally, some children who were assessed as having normal hearing by pediatricians might have had slight or mild hearing loss, or unilateral loss, which went unreported by parents. Moreover, the interaction of various factors, such as genetic predisposition and intrauterine, perinatal, and postnatal influences, could contribute to virus-related damage to the inner ear.

These observations emphasize the relevance of CMV as a cause of hearing loss. This study also supports my study.

Majority of the cases documented in the presented study had birth defects like microcephaly and visual impairment. Other than the major defects there are fever, Purpura, seizures, diarrhea, and pneumonia. The causation of hearing loss due to transmission from mother to child leads to fluctuating to permanent hearing loss. The fact present in the present study concluded beyond doubt that the maternal infection of CMV agent leading to auditory impairment in their unborn children places a burden on to society for unable to prevent such incidences.

Another study was published in 2021.¹⁵ Between December 2012 and November 2018, a total of 401 patients were randomized to receive either dexamethasone or placebo. The median length of stay was shorter in dexamethasone group compared to the placebo group ($p=0.033$). The admissions to ICU were less in the dexamethasone group (3%) than in the placebo group (7%; $p=0.030$). These findings suggested that oral dexamethasone reduces hospital LOS and ICU admission rates in adult patients with CAP.

Another study¹⁶ determined that a 7-day course of adjunctive low-dose steroids in patients with CAP accelerates clinical recovery and reduces the risk of sepsis-related complications. It significantly decreases the duration of mechanical ventilation, intravenous antibiotic use, and hospital stay, leading to improved hospital outcomes and enhanced weaning success from mechanical ventilation. The findings of this study are in agreement with those of current study.

A meta-analysis¹⁷ of various clinical trials concluded that glucocorticoids can reduce mortality in patients with SCAP, with their effectiveness potentially influenced by the specific type used and whether the treatment is tapered. Moreover, glucocorticoid

therapy may shorten the duration of mechanical ventilation. Various other similar meta-analyses¹⁸⁻²¹ have been conducted and all of them have observed the benefits of corticosteroids in the patients of CAP in terms of decreasing the duration of antibiotics administration and hospital LOS. The observed benefits were more pronounced among the patients who had severe disease. And the finding of those meta-analyses is similar to those we observed in current study. In short, a 7-day course of adjunctive corticosteroids therapy can significantly improve prognosis and decrease morbidity and mortality among the patients of SCAP.

5. CONCLUSION

In conclusion, congenital CMV infection plays a major role as a cause of bilateral and unilateral SNHL in children that was hospitalized and follow up in Children's Hospital Lahore. Present study also shows that sensorineural hearing loss in pediatrics is due to congenital cytomegalovirus infection.

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