ISSN: 3032-3134 (ONLINE)
InaJBCS | Indonesian Journal of Biomedicine and Clinical Sciences

The role of toxoplasma, rubella, cytomegalo virus, herpes virus infection as a risk factor for sensory hearing loss in children

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https://doi.org/10.22146/inajbcs.v56i4.15721

Submitted: 2024-08-13
Accepted : 2024-08-26

ABSTRACT

Toxoplasma, rubella, cytomegalovirus and herpes virus infection (TORCH) are syndromes that are considered risk factors for deafness.. This study aims to prove the risk factors which play the most significant role in the incidence of Sensory Hearing Loss in children. This used a case-control design, conducted at JIH Yogyakarta Hospital started from December 2023 to June 2024. All participants aged less than 5 years underwent oto-acoustic emission (OAE) examination, then determined presence or absence toxoplasma, rubella, cytomegalovirus and herpes virus using the electrochemiluminescence immunoassay (ECLIA) method. The inclusion criteria for the case group were: 1) patients diagnosed with sensory hearing loss (SHL), while the control group was normal. The exclusion criteria for the case and control groups there were non-infectious risk factors. Based on a type I error of 5% and type II error of 20%. The recommended sample size is 18 samples per group. Statistical analysis used stratified statistical analysis. The results of this study show that the combination of rubella + CMV had the greatest odds ratio (OR: 8) of sensory hearing loss, CMV OR: 0.62, herpes simplex virus OR: 0.28, combination of rubella + herpes simplex virus OR: 0.28, toxoplasma + CMV OR: 0.28, rubella obtained OR: 1 .5, and the combination of rubella + CMV + herpes simplex virus OR: 0.1. Based on these results the combination of rubella + CMV had the greatest OR compared to the combination of other risk factors and single risk factor.

ABSTRAK

Infeksi toxoplasma, rubella, cytomegalovirus dan virus herpes (TORCH) adalah sindroma yang dianggap sebagai faktor risiko tuli pendengaran. Penelitian ini bertujuan untuk membuktikan faktor risiko yang berperan paling signifikan dalam kejadian *sensory hearing loss* (SHL) pada anak. Penelitian ini menggunakan desain kasus kontrol, yang dilakukan di Rumah Sakit JIH Yogyakarta dimulai dari Desember 2023 sampai Juni 2024. Seluruh peserta berusia kurang dari 5 tahun, menjalani pemeriksaan *oto-acoustic emission* (OAE), kemudian untuk menentukan ada atau tidaknya toxoplasma, rubella, cytomegalovirus dan virus herpes dilakukan pemeriksaan laboratorium metode *electrochemiluminescence immunoassay* (ECLIA). Kriteria inklusi kelompok kasus adalah: 1) pasien yang didiagnosis sebagai SHL, sedangkan kelompok kontrol pendengaran normal. Kriteria eksklusi kelompok kasus dan kontrol jika didapatkan faktor risiko non-infeksi. Berdasarkan kesalahan tipe I sebesar 5% dan kesalahan tipe II sebesar 20%, jumlah sampel minimal adalah 18 sampel setiap kelompok. Penelitian ini menggunakan analisis statistik stratifikasi. Hasil penelitian didapatkan kombinasi rubella + CMV memiliki *odds ratio* (OR: 8) sebagai faktor risiko terbesar SHL, CMV OR: 0,62, OR virus herpes simpleks: 0,28, OR kombinasi virus rubella + herpes simpleks: 0,28, OR toxoplasma + CMV: 0,28, OR rubella: 1,5, dan OR kombinasi virus rubella + CMV + herpes simpleks: 0,1. Berdasarkan hasil tersebut, kombinasi rubella + CMV memiliki OR terbesar dibandingkan dengan kombinasi faktor risiko lain maupun faktor risiko tunggal.

Keywords:
sensory hearing loss;
toxoplasma;
rubella;
cytomegalovirus;
herpes virus

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INTRODUCTION

Hearing loss is the most common sensory disorder in the human population, affecting more than 250 million people worldwide. In the world, according to WHO estimation, in 2005 there were 278 million people suffering from hearing loss, and 75 – 140 million of whom were in Southeast Asia. From the results of the WHO Multi-Center Study in 1998, Indonesia is among the four countries in Southeast Asia with a fairly high prevalence of deafness (4.6%), the other three countries are Sri Lanka (8.8%), Myanmar (8.4%) and India (6.3%) (World Health Organization, 2006).[1]

Congenital deafness is a serious problem in the world of medicine, especially regarding the growth and development of children. It is estimated that it occurs in 1/1000 newborns.[2] This hearing loss causes delays in speech and language development.[3]

Toxoplasmosis, rubella, cytomegalovirus and herpes virus (TORCH) infections, hyperbilirubinemia; craniofacial anomalies; syndrome associated with hearing impairment and severe asphyxia at birth (APGAR <7 at 5 min) is thought to be related to nerve damage. Based on medical record data from Dr. Sardjito General Hospital, Yogyakarta during 2014, 22 outpatients aged 2-5 yr, 28 outpatients aged 0-2 yr, and 15 inpatients aged 0-2 yr were diagnosed with hearing/sensory hearing loss (SHL) and sensorineural hearing loss (SNHL). Research that has been frequently reported proves the existence of risk factors for TORCH infection in the incidence of sensorineural hearing loss.[4]

Until now, research has rarely been conducted on TORCH infections, which play the biggest role in the incidence of SHL in children. This study aims to determine the TORCH component as a risk factor that plays the biggest role in the incidence of SHL in children.

MATERIALS AND METHODS

Study design

This study was observational analytic a case-control research design. The study began by identifying the group with SHL as the case group, and the normal hearing as control group, then examined the presence or absence of TORCH as risk factors.

Time and location

This research conducted at JIH Hospital Yogyakarta after obtaining approval from the Ethics Commission of the Faculty of Medicine, Islamic University of Indonesia Yogyakarta number: 5/Ka.Kom.Et/70/KE/11/2024, from December 2023 to April 2024.

Population and samples

The target population is pediatric patients aged less than 5 yr. Parents of all samples signed an agreement to participate in this research. Each sample underwent an OAE examination for the diagnosis of SHL as a case group and normal hearing as a control group, then an examination was carried out for toxoplasma, rubella, cytomegalovirus and herpes virus in the laboratory of JIH Yogyakarta Hospital. All research subjects were populations that met the inclusion and exclusion criteria. The inclusion criteria for the case group were: results of OAE examination was “refer” as SHL. In the control group, the results of the OAE examination was “pass” as normal hearing. TORCH examination

was carried out on the case and control groups. The exclusion criteria for the case and control groups were non-infectious risk factors (hyperbilirubinemia, LBW, prematurity, asphyxia). The research began by identifying groups suffered from SHL as a case group, and normal hearing as a control group used OAE, then a laboratory examination was carried out using the electrochemiluminescence immunoassay (ECLIA) method to determine there or not TORCH was a risk factor.

Samples

Based on a type I error (α) of 5% for a two-way hypothesis, a type II error (β) of 20%, the recommended number of samples is 18 samples per group, so the total number is: 36 samples, then analyzed using multilevel statistical analysis with using the WinPEPI program.

Statistical analysis

The statistical test used in this study was stratification analysis used WinPEPI program.

RESULTS

In this study it was found that all samples were identified as a combination of rubella + CMV, rubella + CMV + herpes simplex virus, toxoplasma + CMV, the others were single risk factor, namely: rubella, CMV. The highest frequency found in the case and control group samples was CMV. In the case group there were 15 (83.3%) cases, 7 (38.9%) cases of the combination of CMV + rubella, and 2 (11.1%) cases of the combination of CMV + rubella + herpes simplex virus. In the control group there were 12 (66.7%) single cases of CMV, 1 (0.6%) case of the combination of CMV + rubella, and 1 (0.06%) case was the combination of CMV + toxoplasma (TABLE 1).

TABLE 1. Sample distribution of case and control groups

Characteristics	Case group	Control group	p	OR
Age (months)	2 - 60	3 - 60	1	1
Gender				
• Male	12	12	1	1
• Female	6	6	1	1
Rubella + CMV	7	1	0.13	8
CMV	5	12	0.06	0.62
Herpes simplex virus	0	3	0.1	0.28
Rubella + herpes simplex virus	0	1	0.1	0.28
Toxoplasma + CMV	1	1	0.1	0.28
Rubella	3	0	0.7	1.5
Rubella + CMV + herpes simplex virus	2	0	0.1	0.1
Total	18	18		

Note: CMV: cytomegalovirus

DISCUSSION

This study showed that the children suffering combination of rubella + CMV have the highest risk of SHL (OR: 8). The incidence of SHL in children suffering from CMV was 5 (OR: 0.62), from herpes simplex virus was (OR: 0.28), the combination of rubella + herpes simplex virus was 0 (OR: 0.28), toxoplasma + CMV was (OR: 0.28), acquired rubella was 3 (OR: 1.5), and the combination of rubella + CMV + herpes simplex virus 2 (OR: 0.1).

It is presupposed that hearing loss in congenital toxoplasmosis is due to a postnatal inflammatory response. Cysts of *Toxoplasma gondii* were identified in the internal auditory canal, spiral ligament, stria vascularis, and saccular macula of the inner ear. Hearing loss can be secondary to preventable delayed reactivation from the cystic to the active tachyzoite form. During pregnancy, transplacental transmission from the mother to the foetus may occur, and when occurring in early pregnancy, inflammation and necrosis can be observed, particularly in the fetal CNS. Most newborns with congenital toxoplasmosis have subclinical infections at birth. Although hearing loss related to congenital toxoplasmosis has been reported in several studies its pathophysiology remains unclear.[5]

Hearing loss in congenital toxoplasmosis is thought to be caused by a postnatal inflammatory response. A *T. gondii* cyst was identified in the internal auditory canal, spiral ligament, stria vascularis, and saccular macula of the inner ear. Hearing loss may be caused by delayed reactivation of the cystic form of tachyzoites to the preventable active form of tachyzoites. During pregnancy, transplacental transmission from mother to fetus can occur, and if it occurs early in pregnancy, inflammation and necrosis can occur, especially in the fetal CNS. Most newborns with congenital toxoplasmosis have subclinical infections at birth. Although hearing loss associated with congenital toxoplasmosis has been reported in several studies, the pathophysiology remains unclear.[5]

The prevalence of congenital infection with *T. gondii* is estimated at 1 to 10,000 live births in the United States, with few symptoms in the majority of cases. Fetal infections vary from around 15% in the first trimester, 30% in the second trimester, and 60% in the third trimester.[6] At birth, 90% of babies with congenital toxoplasmosis show no signs or symptoms, but who are infected even if they don't show symptoms and signs may develop and progress later in life such as chorioretinitis.[7]

Toxoplasma infection spreads to humans through oocysts in food contaminated with cat feces or undercooked meat products (e.g. pork and lamb) containing cysts. Approximately 85% of women of childbearing age in the United States are seronegative and therefore susceptible to primary toxoplasma infection.[4]

Rubella virus is an RNA togavirus that is transmitted from person to person through inhalation. Rubella infection can be seen as a rubella triad, namely congenital deafness, congenital cataracts, and heart defects.[8] Around 90% of babies who experience prenatal rubella infection before the first 11 wk of pregnancy will show sequelae. Meanwhile, if you get an infection at 11-20 wk of gestation, around 50% of people will show symptoms. After 20 wk of gestation, congenital defects are rare.[4]

If rubella is acquired during pregnancy, it may be associated with fetal hearing loss, congenital cataracts, microcephaly, intellectual disability, thrombocytopenia, heart defects, and skin rashes. Sensorineural hearing loss occurs in 58% of cases of congenital rubella infection. This occurs more often when rubella infection in the mother occurs in the first trimester of pregnancy. This virus causes direct cochlear damage

and cell death in the organ of Corti and stria vascularis.[9]

Infection during pregnancy is an alarming global public health problem. The placenta is an important organ in the mother-fetus interface, responsible for the supply of oxygen/nutrients to the embryo, regulation of the mother's immune system, and protection against infectious agents. Various viruses, bacteria, protozoa, and fungi can cross the transplacental barrier and affect the fetus before birth, thereby disrupting intrauterine growth and causing spontaneous abortion or premature birth. Some pathogens, such as rubella, varicella, toxoplasmosis, and human cytomegalovirus. Among the major abnormalities identified in fetuses and neonates affected by congenital infections are central nervous system (CNS) damage, microcephaly, hearing loss, and eye abnormalities, all of which require regular follow-up to monitor developmental phenotypes. The virus reaches and infects the inner ear through the blood during viremia or through cerebrospinal fluid reaching the cochlear perilymph space or internal auditory meatus.[6,9]

A study of children in Brazil showed that 21% of hearing loss was caused by vertical transmission of the rubella virus, and the incidence of deafness in children whose mothers suffered from rubella during pregnancy was close to 30%. Most cases manifest as severe bilateral hearing loss. In addition to congenital hearing loss, deafness has also been reported to occur in the first year of life. This hearing loss may be caused by direct damage by the virus, because pathological examination found sporadic cell damage in the inner ear, especially in the cochlea and stria vascularis, and damage to the stria vascularis can cause disease. Changes in endolymphatic composition.[5,7,10]

Histopathologically, the temporal bone in deafness due to rubella infection shows changes in the cochleosacular area, while the utricle, semicircular canal and ganglion are usually not affected. The tectorial membrane is found to roll and float within the sulcus. Saccular collapse in the presence of acute inflammation was found in some cases. The organ of Corti is relatively unaffected, but the stria vascularis is often abnormal with cystic dilatation of Reissner's membrane and spiral ligament.[4]

Hearing loss can be caused by congenital CMV (cCMV) infection. This disease occurs in around 10-15% of infected children and can be unilateral or bilateral. Hearing loss associated with CMV infection varies from mild to severe. About half of hearing loss due to cCMV infection is slow or progressive. This infection cannot be detected at birth. Congenital CMV infection is the main cause of sensorineural hearing loss (SNHL), occurring in 30–65% of children with symptoms at birth and 7–15% of children with asymptomatic infection. In both cases, it is an important cause of permanent bilateral hearing loss (PBHL) which is classified as conductive, sensorineural and mixed. Conductive hearing loss originates from disorders in the middle ear that prevent sound transmission efficiently throughout the outer ear canal to the eardrum through the ear bones. Sensorineural hearing loss is caused by damage to the inner ear or auditory nerve and is permanent.[6]

Studies in CMV-infected murines showed that some changes could be seen in spiral ganglion neurons, but not in cochlear hair cells. Researchers found cochlear hair cells decreased after being cleared of the virus, indicating that SNHL caused by the virus was the result of an immune response.[11]

Asymptomatic and symptomatic newborns with cCMV are at risk for long-term neurodevelopmental disorders, such as SNHL, visual impairment, cerebral palsy, autism spectrum disorder, and intellectual disability. Much

research has been conducted regarding this public health problem, cCMV infection remains the main non-genetic cause of SNHL in children in developed countries. Congenital CMV is thought to be responsible for HL in asymptomatic and symptomatic newborns with cCMV who are at risk of long-term neurodevelopmental disorders, such as SNHL, visual impairment, cerebral palsy, autism spectrum disorders, and intellectual. Disabled. Although much research has been conducted on this important public health issue since then, cCMV infection remains the leading non-genetic cause of SNHL in children in developed countries. Congenital CMV is thought to be responsible for HL in one of five cases of children with hearing loss factors without other known risks. A possible pathogenetic hypothesis is that CMV infection of the marginal cell layer of the stria vascularis may alter the circulation of potassium and ions, eliminating endocochlear potential due to cell degeneration of the hair organ of Corti. Paradoxically, hair cells appear to be spared from CMV infection.[12,13]

A study in animal models infected with HSV showed loss of outer hair cells in the scala media, fibrosis in the scala tympani and vestibule, as well as atrophy of the stria vascularis and tectorial membrane. The virus capsid is found within the afferent and efferent nerve fibers of the cochlea, and the virus antigen is found throughout the cochlea. These findings are very similar to studies of human temporal bones in patients with hearing loss after known infection with rubella or measles viruses.[9,14]

Esaki *et al.*[15] reported studies by inoculating HSV-1 or HSV-2 directly into the middle ear in a viral maze mouse model and showed that HSV caused sudden hearing loss and vestibular neuritis. Apoptosis of many cells that did not infect the organ of Corti was found. Detecting the presence of HSV antigen in the stria vascularis of mice. This research shows that HSV infection damages the organ of Corti and its supporting structures causing deafness in mice.[15]

In this study, it is proven that the combination of rubella + CMV infection has the highest risk of SHL compared to single or combination infections. Currently, there has never been a study that proves that combined rubella + CMV infection has a higher risk of SHL than single or combination infection, so further research is needed on this matter.

CONCLUSION

In conclusion, the combination of rubella + CMV infection has highest risk of SHL compared to a single or combination of other infections.

ACKNOWLEDGMENTS

The researchers would like to thank the volunteers and parents of this study. The researchers would also like to thank the Dean and Staff of the Faculty of Medicine, Islamic University of Indonesia Yogyakarta who have facilitated this research, the Main Director of JIH Hospital Yogyakarta and all research assistants who have participated in this research, as well as the Ethics Commission of the Faculty of Medicine, Islamic University of Indonesia Yogyakarta who have provided permission and approval for this research.

REFERENCES

1. World Health Organization. Primary ear and hearing care: training manual. Training material. https://www.who.int/publications/i/item/9789240069152. 2023. WHO Press.
2. Dedhia K, Kitsko D, Sabo D, Chi DH. Children with sensorineural hearing loss after passing the newborn hearing screen. JAMA Otolaryngol

Head Neck Surg 2013; 139(2):119-23. https://doi:10.1001/jamaoto. 2013.1229
3. Lynn MK, Aquino MSR, Self SCW, Kanyangarara M, Campbell BA, Nolan MS. TORCH congenital syndrome infections in Central America's Northern Triangle. Microorganisms 2023; 11(2):257. https://doi.org/10.3390/microorganisms11020257
4. Bailey BJ. Head & Neck Surgery-Otorhinolaryngology. 5th ed. Philadelphia: Williams & Wilkins. 2014; 2170-87.
5. Capra D, DosSantos MF, Sanz CK, Filha LGA, Nunes P, Heringer M. Pathophysiology and mechanisms of hearing impairment related to neonatal infection diseases. Microbiology 2023; 14:1162554. https://doi.org/10.3389/fmicb.2023.1162554
6. Sarvi S, Chegeni TN, Sharif M, Montazeri M, Hosseini SA, Amouei A, *et al*. Congenital toxoplasmosis among Iranian neonates: a systematic review and meta-analysis. Epidemiol Health 2019; 41:e2019021.
7. Salomè S, Malesci R, Cave VD, Amitrano A, Gammella R, Fanelli F, *et al*. Congenital toxoplasmosis and audiological outcome: from a case series to a suggestion of patient-based schedule. Front Pediatr 2024; 11:1297208. https://doi.org/10.3389/fped.2023.1297208
8. Xuong NT, Tran VD. Risk factors of hearing loss among preschool children in Hanoi, Vietnam. Int J Comm Med Public Health 2024; 6(7). https://doi.org/10.18203/2394-6040.ijcmph20192597
9. Shi X, Liu X, Sun Y. The pathogenesis of cytomegalovirus and other viruses associated with hearing loss: recent updates. Viruses 2023; 15(6):1385. https://doi.org/10.3390/v15061385
10. Chen X, Fu YY, Zang TY. Role of viral infection in sudden hearing loss. J Int Med Res 2019; 47(7):2865-72. https://doi.org/10.1177/0300060519847860
11. Aldè M, Binda S, Primache V, Pellegrinelli L, Pariani E, Pregliasco F, *et al*. Congenital cytomegalovirus and hearing loss: the state of the art. J Clin Med 2023; 12(13):4465. https://doi.org/10.3390/jcm12134465
12. Boppana SB, Ross SA, Fowler KB. Congenital cytomegalovirus infection: clinical outcome. Clin Infect Dis 2013; 57(Suppl 4):S178-81. https://doi.org/10.1093/cid/cit629
13. Akpan US, Pillarisetty LS. Congenital cytomegalovirus infection. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. 2023.
14. Kun-Varga A, Gubán B, Miklós V, Parvaneh S, Guba M, Szűcs D, *et al*. Herpes simplex virus infection alters the immunological properties of adipose-tissue-derived mesenchymal-stem cells. Int J Mol Sci 2023; 24(15):11989. https://doi.org/10.3390/ijms241511989
15. Zhao Z, Liu X, Zong Y, Shi X, Sun Y. Cellular processes induced by HSV-1 infections in vestibular neuritis. Viruses 2024; 16(1):12. https://doi.org/10.3390/v16010012