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Susceptibility of congenital or acquired TORCH-infected children to neurodevelopmental disorders: A cross -sectional study at Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Semiramis Zizlavsky[1,*], Tjhin Wiguna[2], Raden Ayu Anatriera[1], Muchtaruddin Mansyur[3], Natasha Supartono[1]

1. Department of Otorhinolaryngology Head & Neck Surgery, Cipto Mangunkusumo General Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
2. Department of Mental Health, Cipto Mangunkusumo General Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
3. Department of Occupational Medicine, Cipto Mangunkusumo General Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

*Correspondence: Semiramis Zizlavsky

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ABSTRACT

Background: *Congenital and acquired TORCH (Toxoplasmosis, Other agents, Rubella, Cytomegalovirus, and Herpes simplex) infections, are associated with hearing impairment and several chronic neurodevelopmental disorders. However, existing evidence on the association between TORCH infections and attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) remains equivoca. This study was performed to investigate the susceptibility of TORCH-infected children to neurodevelopmental disorders.*

Methods: *A cross-sectional study was conducted involving 72 children aged 3-6 years with a history of TORCH infections. ADHD and ASD were assessed using the Indonesian ADHD Rating Scale (IARS) and Modified Checklist for Autism in Toddlers (M-CHAT). TORCH infections were categorized as congenital or acquired, with congenital TORCH defined by persisting positive IgM results at birth or supportive clinical findings and acquired TORCH by the first positive TORCH result after 12 months of age.*

Results: *In this study, most subjects had single infections of Rubella, CMV, or a combination of both, with few findings of toxoplasmosis and HIV. Congenital and acquired TORCH infections were reported*

in 38 (52.7%) and 34 (47.2%) children, respectively. Among congenital TORCH infections, 47.3% had single Rubella infections, while in acquired infections, 11 children had both CMV and Rubella, 9 had single CMV infections, and 5 had single Rubella infections. Rubella and CMV were the most prevalent etiologies in both groups, with 81.9% of children at moderate-to-high risk of ASD and 68.2% at high risk of ADHD. Hearing-impaired children were 3.5 times more likely to develop ADHD (OR 3.5, 95% CI: 1.2-10.3, p=0.021). Among them, the risk of ADHD was 1.4 times higher in those with acquired TORCH infections compared to congenital TORCH (p=0.025) according to subgroup analysis.

Conclusion: *Children with hearing impairment especially acquired TORCH infections are more susceptible to developing ADHD higher than in those with congenital TORCH infection or normal hearing peers.*

Key words: child, neurodevelopmental disorders, TORCH infection, hearing loss

Introduction

Neurodevelopmental disorder is a cognitive and behavioral disorder caused by disruptions in brain development during infancy and early childhood, resulting in impairments in intellectual, motor, and/or social functions [1,2]. The severity of the disorder varies widely, ranging from mild learning difficulties to severe cognitive and mental retardation. According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, neurodevelopmental disorder encompasses autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), neurodevelopmental motor disorders, and specific learning disorders. To date, no specific biomarker has been found to detect these neurodevelopmental disorders; hence, diagnosis must to be made clinically based on the developmental delays [2].

TORCH complex, an umbrella term for toxoplasmosis, others (e.g., parvovirus B19, varicella, syphilis, or hepatitis B), rubella, cytomegalovirus (CMV), and herpes simplex virus infections, represents infections occurring in developing fetuses and newborns in utero (congenital), during delivery, or postpartum (acquired). The signs and symptoms of TORCH infections vary widely depending on the causative organism [3]. Among the organisms in the TORCH family, CMV is one of the most common causes of infection, with the prevalence of congenital infections ranging from 0.2% to 2.0% (average prevalence: 0.65%). The high prevalence of this disease, characterized by its classical triad of microcephaly, chorioretinitis, and intracranial calcification, is attributed to high maternal seroprevalence [4]. A study conducted at the neonatal intensive care unit of the Department of Pediatrics, Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia, reported a congenital CMV seroprevalence of 5.8% [5]. In addition to CMV, rubella virus is another commonly reported cause of the TORCH infections, with an incidence of 1/1500 live births of congenital rubella syndrome (CRS) in Yogyakarta (Central Java, Indonesia) in 2017 [6]. This is similar to the incidence reported in the neighboring country of Vietnam of 2.1/1000 live births in 2011 [7]. In children, CMV infection have a strong association with sensorineural hearing loss (SNHL), with an estimated prevalence of 33-65% [8,9]. The degree of SNHL varies considerably from negligible hearing loss to total bilateral deafness [9]. However, the exact mechanism have

not been elucidated fully.

Congenital hearing loss due to CMV infection could be mediated by the chronic progressive destruction of the central nervous system (CNS) [8]. Microscopically, the virus disrupts the regulation of glutamate, an essential dopaminergic neurotransmitter vital to the development of cognitive and behavioral skills [10]. CMV is one of the most prevalent infectious diseases worldwide, with a global prevalence of 0.2-2.2%, of which approximately 85-90% cases are asymptomatic [11]. Previous studies have revealed that the risk of developing ASD is 10 times higher in children with congenital CMV infection than in healthy children [12]. Rubella in pregnancy also linked to autism [13]. A study in Italy reported that approximately 5.3% of the children with ASD had a history of CMV infection [12].

Methodology

TORCH is divided as congenital and acquired. Congenital TORCH is defined as positive IgM result from birth and persists up until 12 months or supportive clinical findings were found, whereas acquired TORCH is defined as first positive TORCH result at more than 12 months of age.

In this study, majority of the subjects have single infection of Rubella, CMV or combination of both, there were few findings of toxoplasmosis and HIV. Congenital and acquired TORCH infections were reported in 38 (52.7%) and 34 (47.2%) children. Amongst congenital TORCH Infection, single rubella infections were detected in 18/38 children (47.3%), single CMV were found in 5 children, and combination of CMV and Rubella infections were found in 7 children. Meanwhile in acquired TORCH infections, 11 children had both CMV and Rubella, 9 children had single CMV infections and 5 children had single rubella infections. Both groups shows that Rubella and CMV infections are two most prevalent etiology of TORCH in this study.

This cross-sectional study was conducted from January 2021 to January 2022 in the Ear, Nose, and Throat outpatient clinic of the Department of Otorhinolaryngology and Head and Neck Surgery, Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia. Inclusion criteria were children aged 3-6 years with a history of TORCH infections, who visited the outpatient clinic for hearing screening, were consecutively recruited in this study. The children were divided into two groups based on prenatal TORCH infections (congenital TORCH infection) and TORCH infections occurring after birth (acquired TORCH infection). Children with other comorbidities that might confound the association between TORCH infections and neurodevelopmental disorders were excluded. Sample size calculation with two independent proportions revealed that a minimum of 32 patients were required in each group. The children's parents provided informed consent for study participation. All children underwent otoacoustic emission (OAE) and brainstem evoked response audiometry (BERA) tests. The OAE pass result and BERA detected up to 20 dB indicates normal hearing. Diagnoses were made independently by experienced psychiatrist and ENT consultant. Their parents were interviewed to collect the necessary information about the children and complete the Indonesian ADHD Rating Scale (IARS/*Skala Penelitian Perilaku Anak Hiperaktif Indonesia*) and Modified Checklist for Autism in Toddlers (M-CHAT) questionnaires [14].

Briefly, the IARS questionnaire screens for ADHD using 35 four-point Likert scale items scored from "never or seldom" (score 0) to "always" (score 3), with a maximum score of 150. A total score ≥30 indicates that the children are at a high risk of developing ADHD, if the parents have completed the questionnaire. In contrast, the M-CHAT questionnaire screens for ASD using 23 yes/no questions, with a maximum score of 23. Based on the scores, the risk of developing ASD is categorized as low (0-2), moderate (3-7), and high (≥8). Parents who were illiterate in Bahasa Indonesia were assisted by an interpreter to complete the questionnaires.

The collected data were computed in Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA). Statistical analyses were conducted using Statistical Product and Service Solutions (version 26.0; SPSS Inc., Chicago, IL, USA). Dichotomous data are presented as frequencies and proportions, while continuous data are presented as medians and interquartile ranges. Differences between the groups were analyzed using Pearson's chi-square or Fisher's exact tests for dichotomous variables and the Mann–Whitney U test for continuous variables. The association between the onset of TORCH infections and IARS scores, stratified by the children's hearing ability, was analyzed using the Mantel–Haenszel statistics and presented as odds ratios (OR) with their 95% confidence intervals (CI). Statistical significance was set at two-tailed p-values ≤0.05.

The study protocol was approved by the Health Research Ethics Committee of Dr. Cipto Mangunkusumo National General Hospital, Faculty of Medicine, Universitas Indonesia (ethical clearance no. KET-881-UN2.F1/ETIK/PPM.00.02/2020).

Results

This study included 72 children (56 boys and 16 girls). The proportion of girls with congenital TORCH infection was higher than that of boys (75.0% vs. 48.2%), whereas the converse was true for acquired TORCH infection (boys vs. girls: 51.8% vs. 25.0%). Most children were aged between 4-6 years (58.3%), with congenital TORCH infections being the most common in children aged 4-6 years (60.5%) and acquired TORCH infections in those aged 4-6 years (18.2%). Approximately 66.7% of the children had hearing loss. The incidence of hearing loss in children with congenital TORCH infections was significantly higher (P <0.00001) than that in children with acquired TORCH infections (**Table 1**).

Table 1. Subjects' Characteristics

Characteristics	N = 72 (%)	Congenital TORCH infections, % (n=38)	Acquired TORCH infections, % (n=34)	P value
Sex				**0.180**
Male	**56 (77.8)**	**27 (71.1)**	**29 (85.3)**	
Female	**16 (22.2)**	**11 (28.9)**	**5 (14.7)**	
Age (years)				**0.925**
0-3	**26 (36.1)**	**13 (34.2)**	**13 (30.3)**	
4-6	**42 (58.3)**	**23 (60.5)**	**19 (18.2)**	

>6	4 (5.6)	2 (5.3)	2 (51.5)	
Hearing level				<0.0001
Normal	24 (33.3)	2 (5.3)	22 (64.7)	
Hearing Loss	48 (66.7)	36 (94.7)	12 (35.3)	
Bilateral AN Unilateral Mild CHL Bilateral Mild CHL Unilateral Profound SNHL Bilateral Profound SNHL	3 (4.2) 1 (1.4) 2 (2.8) 1 (1.4) 39 (54.2)	3 (7.9) 0 0 1 (2.6) 32 (84.2)	0 1 (2.9) 2 (5.9) 0 7 (20.6)	
Right Ear Moderate SNHL – Left Ear Profound SNHL	1 (1.4)	0	1 (2.9)	
Right Ear Profound SNHL – Left Ear Severe SNHL	1 (1.4)	0	1(2.9)	
TORCH Infections				0.06
Toxoplas-mosis Rubella CMV HSV Measles Rubella & CMV Rubella & Toxoplas-mosis Rubella & Measles CMV & HSV CMV & Toxoplas-mosis Rubella, CMV, Tox-oplasmosis Rubella, CMV, HSV	1 (1.4) 23 (31.9) 14 (19.4) 1 (1.4) 2 (2.8) 18 (25) 2 (2.8) 1 (1.4) 2 (2.8) 1 (1.4) 4 (5.6) 3 (4.2)	1 (2.6) 18 (47.4) 5 (13.2) 0 0 7 (18.4) 1 (2.6) 1 (2.6) 0 1 (2.6) 2 (5.3) 2 (5.3)	0 5 (14.7) 9 (26.4) 1 (2.9) 2 (5.9) 11(32.4) 1 (2.9) 0 2 (5.9) 0 2 (5.9) 1 (2.9)	

Table 1. Characteristics of the children stratified by the onset of TORCH infections

Abbreviations: TORCH, toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex infections

Following subject characteristics, **Table 2 will show results of M-CHAT score and IARS score in both groups.**

Category	N (%)	M-CHAT score			P-value	IARS score		P-value
		0-2	3-7	≥8		<30	≥30	
Congenital TORCH infections	38 (52.3)	6 (15.7)	18 (47.4)	14 (36.8)	0.759	12 (31.5)	26 (68.5)	0.484
SEX			13	11	0.308			0.0001
Male		3	5	3		8	19	
Female		3				4	7	
ETIOLOGY								
Toxoplasmosis		0	1	0		1	0	
Rubella		4	5	9		11	7	
CMV		2	2	1		3	2	
HSV		0	0	0		0	0	
Measles		0	0	0		0	0	
Rubella & CMV		0	5	2		4	3	
Rubella & Toxoplasmosis		0	1	0		1	0	
Rubella & Measles		0	1	0		0	1	
CMV & HSV		0	0	0		0	0	
CMV & Toxoplasmosis		0	0	1		1	0	
Rubella, CMV, Toxoplasmosis		0	2	0		2	0	
Rubella, CMV, HSV		0	1	1		1	1	
Acquired TORCH infections	34(47.7)	7 (20.6)	17(50)	10 (29.4)	0.863	9 (26.5)	25 (73.5)	0.591
SEX				9	0.451			0.038
Male		6	14	1		7	22	
Female		1	3			2	3	
ETIOLOGY								
Toxoplasmosis		0	0	0		0	0	
Rubella		1	1	3		4	1	
CMV		3	3	3		6	3	
HSV		0	1	0		1	0	
Measles		0	1	1		1	1	
Rubella & CMV		1	7	3		7	4	
Rubella & Toxoplasmosis		0	1	0		1	0	
Rubella & Measles		0	0	0		0	0	
CMV & HSV		1	1	0		1	1	
CMV & Toxoplasmosis		0	0	0		0	0	
Rubella, CMV, Toxoplasmosis		0	2	0		2	0	
Rubella, CMV, HSV		1	0	0		1	0	
Total	72 (100)	13 (18.1)	35 (48.6)	24 (33.3)		48 (66.7)	24 (33.3)	

Table 2. Results of M-CHAT score and IARS score in both groups

Table 2. Susceptibility to autism spectrum disorder and attention deficit hyperactivity disorder in TORCH-infected children

Unless otherwise stated, all data are expressed as numbers (%). Bold text denotes statistical significance.

*Fisher's exact test; #Pearson's chi-squared test

Abbreviations: M-CHAT, Modified Checklist for Autism in Toddlers; **IARS,** Indonesian Attention Deficit Hyperactivity Disorder Rating Scale; **TORCH infections,** toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex infections.

In this research, using the Cochran–Mantel–Haenszel test (CMH), hearing-impaired children were 3.5 times more vulnerable to develop ADHD than the normal-hearing children (OR 3.5, 95% CI: 1.2-10.3, p=0.021) This means that ADHD risk in children with TORCH is higher in the hearing-impaired children compared to their normal-hearing peers. The result of CMH test can be found in Table 3

Table 3. Cochran-Mantel-Haenszel Test Risk Estimate

Odds Ratio For	Value	95% Confidence Interval		P-Value
		Lower Limit	Upper Limit	
Hearing Threshold - IARS Score	**3.5**	**1.2**	**10.3**	**0.021**
TORCH Onset - IARS Score	**1.4**	**0.52**	**3.76**	**0.025**

Unless otherwise stated, all data are expressed as numbers (%). Bold text denotes statistical significance.

*Mantel–Haenszel statistics; #Pearson's chi-squared test

Abbreviations: CI, confidence interval; **IARS,** Indonesian Attention Deficit Hyperactivity Disorder Rating Scale; **OR,** odds ratio; **TORCH,** toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex infections

Then We continue to analyze the relationship between the onset of congenital/ acquired TORCH and ADHD (those who had IARS score of 30 or higher) and we found that there's a relationship between ADHD and TORCH, children with acquired TORCH infection has 1.4 times higher risk (CI: 0.521-3.765, p=0.025) to develop ADHD compared to those who had congenital TORCH infection. In this research, ADHD in TORCH patients have no relationship with the etiology of infection (p=0.716). We also found that the risk of ASD (based on M-CHAT score) in TORCH patient in this research has no relationship with the hearing threshold.

Discussion

Autism Spectrum Disorder (ASD) comprises neurodevelopmental disorders characterized by deficits in social communication skills. Moreover, the presence of a restricted, repetitive pattern of behavior

and interests is one of the leading causes of morbidity in ASD children under 5 years of age [15]. The process of diagnosing ASD is challenging because it is purely based on clinical assessments. Nonetheless, routine ancillary investigations involving genetic and metabolic marker testing are usually performed to exclude the secondary causes of ASD. Genetic testing is recommended in children with hereditary and genetic diseases, intellectual disability, and/or congenital malformations. On the other hand, metabolic panel investigations are recommended in those with a family history of metabolic diseases, cyclical vomiting syndrome, childhood epilepsy, mental retardation, and/or suspicion of inborn errors of metabolism [12]. In some cases, ASD is linked to viral CNS infections or viral infections triggering autoimmune reactions in the brain cells. Recently, the potential roles of inflammation, cytokine dysregulation, and brain-reactive autoantibodies in the development of ASD have gained attention, especially because these processes markedly deter brain development [15, 16].

TORCH infections during pregnancy are a common cause of congenital abnormalities, poor fetal outcomes, and recurrent miscarriages [17]. Congenital TORCH infections, especially CRS and congenital CMV infection, have a strong association with ASD [15, 18]. CMV can directly damage the brain tissues by crossing the blood–brain barrier, impairing the chromosome-modulating gene expression for brain development, impeding neuronal differentiation, and inducing apoptosis of neural precursor cells. Furthermore, CMV can disrupt the CNS by infecting the CD8+ T cells and inducing severe inflammation, which may trigger autoimmune reactions. Approximately 80-90% of the neonates infected with congenital CMV are asymptomatic at birth, of which 10-20% may suffer neurological complications, including SNHL, psychomotor retardation, and epilepsy, in the later stages of life [15]. Moreover, ASD is considered as one of the late-onset neuropsychiatric complications of congenital CMV infection in children. A study showed that approximately 5% of ASD children had congenital CMV infection, which is considerably higher than the prevalence of congenital CMV infection in the general population (0.6%). This finding further reinforces the link between CMV infection and ASD [12].

In addition to CMV infection, rubella virus infection is one of the most common TORCH infections causing ASD. Congenital Rubella Syndrome (CRS) a multiorgan disorder caused by maternal rubella infection during pregnancy, is a debilitating congenital disease resulting in SNHL, cataracts, congenital heart defects, and/or brain and CNS damage [7, 19]. The severity of the CRS manifestation varies widely depending on the onset of the infection during pregnancy, ranging from temporary self-limiting symptoms to permanent disabilities. Some cases remain asymptomatic in childhood and begin manifesting symptoms only after adolescence or adulthood. Nonetheless, neuropsychiatric complications are seen in more than half of children with CRS, with mental retardation and ASD showing a prevalence of 42.0% and 4.1-7.3%, respectively [19, 20]. Additionally, other psychiatric symptoms such as irritability, psychomotor agitation, aggression, and self-harm are commonly observed in children with CRS [19]. Nonetheless, a previous study conducted in French autistic children failed to substantiate this finding. This could partly be explained by the fact that the study, which reported a CRS prevalence of 0.6% among children with ASD, had a small sample size, thus limiting its ability to explore the association between the variables

[20]. The effects of CRS on ASD could be attributed to the maternal rubella-specific antibodies that can cross the placental barrier and damage the fetal brain cells through molecular antigen mimicry, thus stunting brain development [21]. Furthermore, rubella virus may also alter the retinoid metabolism in the liver, subsequently resulting in excessive retinoid buildup in the liver tissues, liver damage, and systemic toxicity of retinoid, especially retinyl ester and retinoic acid. Consequently, this may cause impaired development in multiple fetal organs including the heart, blood vessels, and brain, leading to congenital malformations and impairments as well as miscarriages and stillbirths [13].

To date, evidence of the association between maternal infection and ASD in the offspring has been equivocal. Although some studies have found that any maternal infection may increase the risk of ASD in children [22, 23]. Others have failed to find a significant correlation between maternal viral or bacterial infections and ASD [21]. Although rubella is one of many maternal infections with possible links to autism, b oth CRS and autistic children may develop hyperactivity and spasticity [24]. Nevertheless, the high prevalence of TORCH-infected children susceptible to neurodevelopmental disorders such as ASD and ADHD observed in this study cohort suggests that these conditions should not be overlooked in children with a history of congenital or acquired TORCH infections. Moreover, routine screening for neurodevelopmental disorders in this vulnerable population is warranted.

Conclusion

Children with hearing impairment especially acquired TORCH infections are more susceptible to developing ADHD higher than in those with congenital TORCH infection or normal hearing peers. This warrants routine screening for neurodevelopmental disorders in TORCH-infected children, especially those with acquired TORCH infections.

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Author Contribution

Semiramis Zizlavsky: Conceptualization, Methodology, Supervision, Writing-Original draft preparation, **Raden Ayu**: Investigation, Data curation, Writing, Editing, **Thjin Wiguna**: Investigation, Data curation, **Muchtaruddin Mansyur**: Methodology, Formal Analysis, Reviewing and Editing, **Natasha Supartono** Project Administration, Investigation, Writing, Editing

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