Research Article

Prevalence of Cytomegalovirus Infection among Children with and with out Autism in Jakarta, Indonesia

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Abstract |Cytomegalovirus (CMV) can affect the structural development and functional connectivity of the brain in children with autism. The infection in healthy children is usually mild or asymptomatic, but individuals with weakened immune systems are at higher risk for severe diseases. Study in Egypt showed a high prevalence of CMV IgG (97.8%) in children with autism. In Indonesia, there is no current data available to indicate the prevalence of CMV in children with autism. Therefore, we examined anti-CMV IgG in children with autism and analyzed the relationship between IgG CMV variable and more independent variables. During 2023, 100 children with autism and 101 children without autism (2-5 years old) were offered a CMV antibody test used ELISA (Enzyme-Linked Immunosorbent Assay). Besides of anti-CMV IgG, gender, age in children, we also assessed other parental variables and used linear regression. Seropositivity of CMV in children was found to be 98% (with autism) and 96% (without autism). We identified a strong relationship between IgG CMV (R^2 = 0.041) and children gender (autism group). However, no other statistically significant variable was identified. Taken together, CMV infection in autism had high prevalence (98%) and have relationship with children gender in children with autism group. We found no additional and statistically significant varibles in children without autism group.

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Introduction

Cytomegalovirus (CMV) is frequently discussed in various studies on autism in children (Ornoy *et al*., 2016). CMV infection can be detected through serological examination using the ELISA (Enzyme-Linked Immunosorbent Assay) method. The prevalence of CMV infection in children with autism reaches 50%, including latent CMV infections that reactivate or active infections (Hassan *et al*., 2023). Both primary and recurrent reactivation of CMV can affect the structural development and functional connectivity of the brain in children with autism. The frequency and degree of virus reactivation can influence the severity, impacting neuropathological changes and clinical manifestations in children with autism

(Yang *et al*., 2022).

CMV not only causes congenital disabilities in children but also contributes to developmental delays, including the onset of autism (Maeyama *et al*., 2018). CMV can alter brain development and cause disorders such as brain calcification and developmental disruptions in children with autism (Shuid *et al*., 2021). One of the initial causes of autism is neuroinflammation in the cerebral cortex. The increase in reactive microglia and astrocytes leads to excess neurons, affecting overconnectivity in specific brain areas. Abnormal neuronal migration results in atypical synaptogenesis, causing disruptions in inhibitory signalling networks. These disruptions can lead to sensory processing abnormalities in autistic children (Al-Berltagi *et al*., 2023).

Children with autism who have been infected with CMV exhibit poorer immune system conditions compared to those who have not been infected with CMV. Dysregulation of pro-inflammatory factors in the body, particularly cytokine profiles, has been extensively studied (Kasztelewicz *et al*., 2017). CMV can also induce cytokine-mediated immune responses, facilitating communication between immune cells (Chinta *et al*., 2020). Previous studies have shown that CMV can activate inflammatory cytokine responses and induce signalling to alter cytokine production (Xie *et al*., 2014). CMV infection as a cause of immune system dysregulation in children with autism is still being investigated. CMV-induced cytokine imbalance can inhibit brain nerve growth, posing risks for developmental, communicative, and social function disorders. Additionally, cytokine imbalance can affect the child's immune condition (Maeyama *et al*., 2018).

CMV infection in healthy children is usually mild or asymptomatic, but individuals with weakened immune systems are at higher risk for severe diseases. Children with primary immunodeficiency have a significant risk of severe CMV infection, such as pneumonia, hepatitis, neutropenia, thrombocytopenia, and enterocolitis (Bateman *et al*., 2021). Children with autism have weakened immune systems, with several studies showing a strong correlation between autism and immune dysfunction, leading to behavioural abnormalities (Gładysz *et al*., 2018). Other studies indicate that immune dysfunction in children with autism is a risk factor contributing to neurodevelopmental deficits (Meltzer and Water, 2017). Early neurological development in a cohort of CMV seropositive children can affect neonatal neurological status or early-life development, manifesting as motor abnormalities (Novelli *et al*., 2022).

CMV is the most common cause of congenital infection in children globally. The estimated prevalence rate of congenital CMV (cCMV) is 0.67%, ranging from 0.48% in high-income countries to 1.42% in low- and middle-income countries (Ssentongo *et al*., 2021). Previous research indicated that 21% of children aged 1 to 5 years in the United States are CMV seropositive (Lanzieri *et al*., 2015). Another study found a higher prevalence of CMV IgG antibodies among children aged 6 to 8 years (38%) (White *et al*., 2019). Recent research in Egypt showed a high prevalence of CMV IgG (97.8%) in children with autism examined using ELISA (Hassan *et al*., 2023). In Indonesia, there is no current data available to indicate the prevalence of anti-CMV IgG in children with autism. Therefore, we examined anti-CMV IgG in children with autism and potential risk factors.

Materials and Methods

The study employed a cross-sectional research design, specifically targeting children aged 2-5 years, both with and without autism, as the inclusion criteria. This study encompassed a sample of 201 children divided into two distinct groups: 100 children diagnosed with autism using CARS (The Childhood Autism Rating Scale) and 101 children diagnosed without autism using M-CHAT (Modified Checklist for Autism in Toddler). Data was gathered in Indonesia for three months, specifically from September to December 2023. Each participant was provided with and consented to the informed consent document. Approval for ethical considerations was obtained from the Ethical Committee of the Faculty of Medicine, University of Indonesia (KET824/UN2.F1/ETIK/PPM.00.02/2023).

Sample Collection

EMLA (Eutectic Mixtures of Local Anaesthetics) cream is applied to the child's hand area to induce local anaesthesia and reduce pain perception. A blood sample of approximately 3 mL is collected and transferred into an EDTA tube that contains an anticoagulant. The blood sample is centrifuged at room temperature for 10 minutes at 3500 rpm to obtain serum

plasma and buffy coat. The serum and buffy coat are stored at a temperature of -80°C.

Serological Test

The Enzyme-Linked Immunosorbent Assay (ELISA) technique is utilised for serological analysis of IgG antibodies against CMV. The ELISA kits utilised are designed to detect IgG antibodies specific to CMV (Calbiotech, CM027G). The ELISA method is performed according to the instructions provided by each kit. The plasma was diluted at 1:21 for IgG anti-CMV.

Data Analysis

Data analysis in this study used univariate and bivariate analysis. The univariate analysis consisted of respondent characteristics with mean and frequency distribution. Bivariate analysis in this study used paired t-test with significance level was set at $p<0.05$ (Graph Pad Prism 10, San Diego, CA). We used to calculate the probability of the occurrence of a specific categorical event based on the values of a set of independent variables (IBM SPSS Statistic versi 27.0 SPSS).

Results and Discussion

A total of 201 subjects in the study (Table 1), of which 78% were boys and 22% were girls in autism group and 55% were boys and 44% were girls in autism group. Study at University were the largest parental educational status in both of group. Around 95% father (with autism children) and 98% father (without autism children) had employment. Mother had not employment status were the largest mother employment status in both of group. Of the children (2-5 years old) as subjects, 98% (with autism) and 96% (without autism) were anti-CMV IgG positive.

We examined linear regression model to analyse the relationship between a dependent variable and one or more independent variables. Linear regression can be used to predict the value of the dependent variable based on the values of the independent variables. It quantifies the strength and type (positive or negative) of the relationship between the dependent and independent variables. Based on (Table 2), we found value of IgG CMV (dependent variable) R-Square (R^2) = 0.041 with children gender as independent variable. This value indicates that 4.1% of the variance in IgG CMV scores can be predicted from the variable children gender. The variable children age can be used to reliably predict IgG CMV because p=0.047 (smaller than 0.05). The beta coefficient (β) on the children gender variable (β=-0.202) shows that the lower the differences of gender can be associated with a decrease in anti-CMV IgG.

Table 1: *Description of subjects (N=201).*

Sociodemographic	With autism (N = 100)	Without autism (N = 101)
Children Age, mean (SD)	4.21 (0.73)	3.57 (0.92)
Children Gender, n (%)		
Boy	78 (78.0)	55 (54.5)
Girl	22 (22.0)	46 (45.5)
Anti-CMV IgG n (%)		
Negative	1 (1.0)	0 (0.0)
Boderline	1 (1.0)	5 (5.0)
Positive	98 (98.0)	96 (95.0)
Parental Age, mean (SD)		
Father	36.00 (6.13)	33.74 (3.92)
Mother	33.30 (4.49)	32.08 (3.29)
Parental Educational Status, n (%)		
Father		
University	84 (84.0)	92 (91.1)
Non University	16 (16.0)	9 (9.9)
Mother		
University	81 (81.0)	98 (97.1)
Non University	19 (19.0)	3 (3.9)
Parental Employment Status, n (%)		
Father		
Employment	95 (95.0)	98 (97.1)
Not Employment	5 (5.0)	3 (3.9)
Mother		
Employment	32 (32.0)	44 (43.5)
Not Employment	68 (68.0)	57 (56.5)

We also found R-Square (R^2) = 0.068 to analyze relationship between IgG CMV and age (children and parents). This value indicates that 6.8% of the variance in IgG CMV scores can be predicted from the variable children and parental age. The beta coefficient (β) on the age variable (β=-0.100, -0.021, and -0.022) shows that the lower age can be associated with a decrease in anti-CMV IgG. The p-value of children and father age were greater than 0.05, shows that the group of independent variables does not show a statistically

Table 2: *Linear Regression Model in children with autism seropositive anti-CMV IgG (N=98) for gender, age, educational and employment status.*

	β	T	p	95% CI for β	
				Lower	Upper
IgG CMV: R^2= 0.041, F=0.047					
Children Gender	-0.202	-2.016	**0.047**	-5.320	-0.041
IgG CMV: R^2= 0.068, F=0.085					
Children Age	-0.100	-0.278	0.782	-1.787	1.349
Mother Age	-0.021	-2.273	**0.025**	-0.842	-0.057
Father Age	-0.022	1.227	0.223	-0.108	0.456
IgG CMV: R^2= 0.045, F=0.368					
Mother Educational Status	-0.141	-1.233	0.221	-5.263	1.230
Father Educational Status	-0.023	-0.192	0.848	-4.013	3.305
Mother Employment Status	-0.064	-0.620	0.537	-3.200	1.677
Father Employment Status	-0.101	-0.101	0.340	-7.859	2.743

Bold : p ≤ 0.05 (significant) used multivariate linear regression model

Table 3: *Linear Regression Model in children without autism seropositive anti-CMV IgG (N=96) for gender, age, educational and employment status.*

	β	**T**	**p**	**95% CI for β**	
				Lower	**Upper**
IgG CMV: R^2= 0.015, F=0.238					
Children Gender	0.122	1.188	0.238	-0.804	3.197
IgG CMV: R^2= 0.029, F=0.433					
Children Age	0.041	0.391	0.697	-0.908	1.353
Mother Age	-0.140	-0.908	0.366	-0.658	0.245
Father Age	-0.045	-0.295	0.769	-0.447	0.332
IgG CMV: R^2= 0.014, F=0.856					
Mother Educational Status	0.060	0.561	0.576	-4.285	7.655
Father Educational Status	-0.033	-0.314	0.755	-4.076	2.965
Mother Employment Status	0.044	0.410	0.683	-1.661	2.526
Father Employment Status	-0.080	-0.755	0.452	-9.937	4.462

Bold : p ≤ 0.05 (significant) used multivariate linear regression model

significant relationship with the dependent variable, and does not reliably predict the dependent variable.

Educational and employment status in parents shows R-Square (R^2) = 0.045. That value indicates that 4.5% of the variance in IgG CMV scores can be predicted from the variable educational and employment status in parents. The beta coefficient (β) on the all variable (β=-0.141, -0.023, -0.064, and -0.101) shows that the lower status of education and employment of parents can be associated with a decrease in anti-CMV IgG. The all p-value were greater than 0.05, shows that the group of educational and employment status in parents variables does not show a statistically significant relationship with the IgG CMV, and does not reliably predict the IgG CMV scores.

We also examined linear regression model in children without autism group (Table 3). The all p-value were greater than 0.05, shows that independent variables does not show a statistically significant relationship with the IgG CMV.

If the p-value is greater than 0.05, it indicates that there is not enough evidence to reject the null hypothesis, which typically states that there is no relationship between the independent and dependent variables.

We examined anti-CMV IgG in a group of children aged 2-5 years, consisting of those with autism and those without autism. Our findings indicate a high prevalence of CMV among children aged 2-5 years in Jakarta (Indonesia), both in children with and without autism. In Indonesia, data on CMV prevalence in

children are unavailable; however, some studies have conducted anti-CMV IgG serology tests using adult subjects. One study involved blood donors in Jakarta, where 111 samples (98.23%) tested positive for IgG CMV (Noviar, 2017). A report on CMV prevalence across 72 studies covering 11 countries (Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Oman, Palestine, Saudi Arabia, Sudan, and Tunisia) over 31 years (1988–2019) found CMV seroprevalence in the MENA (Middle East and North Africa) region ranging from 8.7% to 99.2% (SD = 38.95%). The incidence of CMV in these countries ranged from 1.22% to 77% among transplant and blood transfusion recipients (Al Mana *et al.*, 2019).

CMV prevalence is also high among patients with haematological diseases in the Western Brazilian Amazon. The highest rates were found in patients suffering from platelet disorders (94.5%), anaemia (93.3%), or leukaemia (91%) (de Melo Silva *et al.*, 2021). In contrast, in developed countries, CMV prevalence is not as high as in developing countries. In a study that screened anti-CMV IgG in 48 children aged six months to 5 years, 27% were found to be anti-CMV IgG positive (Dollard *et al.*, 2014). A report from 19 studies published from 1980 to 2020, including nine studies from Asia, five from Europe, four from the Americas, and one from Africa, found the prevalence of CMV infection among infants with Biliary Atresia (630 patients) to be 25.4% (Mohamed *et al.*, 2021).

In our study, we found no statistically significant relationship between anti-CMV IgG and sociodemographic factors in the group of children without autism. However, in the group of children with autism, there was a significant relationship between the child's gender and the mother's age. Gender is a primary intrinsic factor influencing the number and function of immune cells. Hormone levels and genes on the sex chromosomes may mediate these effects. Additionally, the impact of persistent viruses may differ between males and females (van der Heiden *et al.*, 2016). Previous publications have indicated that gender differences in immune cell status arise due to the immunomodulatory effects of long-term immunosurveillance pressure to control CMV infection (Di Benedetto *et al.*, 2019). Immunologically, gender differences have been demonstrated in several aspects of HCMV's influence on adaptive immunity, including circulating memory T cell subsets and cytokine profiles (Cox *et al.*, 2020).

Children with (compared to without) congenital CMV (cCMV) diagnosis in Medicaid claims data, most of whom had cCMV symptoms, were more likely to have an ASD diagnosis (hazard ratio: 2.5; 95% confidence interval: 2.0–3.2, adjusting for birth year, sex, and region) (Pesch *et al.*, 2024). Research investigating ASD risk among various groups of children's conditions needs to be identified through CMV screening. This is expected to help elucidate the relationship between CMV and ASD in the future.

Conclusions and Recommendations

In conclusion, our findings confirm the high prevalence of anti-CMV IgG in children with autism in Indonesia. We did not find any statistically significant relationship between anti-CMV IgG and sociodemographic factors in the group of children without autism. However, in the group of children with autism, a significant relationship was found between the child's gender and the mother's age.

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Novelty Statement

This study represents the first investigation in Indonesia that examines the prevalence of IgG anti-CMV in children with autism aged 2-5 years. To date, no similar studies have been conducted in Indonesia, and only limited research has explored the association between CMV and autism globally. This research addresses a significant gap in understanding the role of CMV in children with autism, especially in this critical early age group, providing valuable insights that could contribute to further research in this field.

Authors Contributions

All authors have accepted responsibility for the en-

tire content of this manuscript and consented to its submission to the journal, reviewed all the results and approved the final version of the manuscript. AS and IAA designed the experiments and IA carried them out.

Conflict of Interests

The authors declare that they have no competing interests.

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