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Original Article

Diagnostic value of clinical manifestations of Group A and Group B compared with rubella serology results in congenital rubella syndrome

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Abstract

Background Congenital rubella syndrome (CRS) is the triad of defects/abnormalities in the heart, eyes, and ears, resulting from rubella virus infection, especially in the first trimester of pregnancy. Manifestations of CRS are divided into Group A including: hearing loss, congenital heart disease, cataracts or glaucoma, and pigmentary; Group B consisted of purpura, splenomegaly, microcephaly, mental retardation, retinopathy and icteric, radiolucent bone disoreder, that appears within 24 hours after birth. CRS diagnosis is based on serologic rubella test results. Comprehensive management of CRS is needed to achieve optimal child development. However, not all referral center hospitals in Indonesia have serological rubella examination modalities.

Objective To evaluate the diagnostic value of group A and group B clinical manifestations compared to rubella serology results in the diagnosis of CRS.

Methods This cross-sectional study used secondary data from medical records of pediatric patients with suspected CRS who meet the criteria for groups A and B aged less than 12 months who had been hospitalized at Dr. Zainoel Abidin Regional General Hospital, Banda Aceh, during the three-year study period (2019-2021) which had complete data were included in the study. The IgM serology results were used as diagnostic comparison that performed at the age of less than 12 months.

Results A total of 126 patients met the inclusion criteria. Sixty-five (51.6%) subjects were male, 80 (63.5%) subjects had normal birth weight, and 89 (70.6%) subjects were aged <6 months. The diagnostic sensitivity for groups A, B, as well as A and B clinical manifestations were 100%, 75%, and 100%, respectively. This excellent sensitivity value suggested that the clinical manifestations of groups A and B would be suitable as screening tools because they could "catch" many patients with suspected CRS.

Conclusion The clinical manifestations of group A and group B have excellent diagnostic value as a screening tool for CRS. **[Paediatr Indones. 2024;64:139-44; DOI: 10.14238/pi64.2.2024.139-44]**.

Keywords: *congenital rubella syndrome; rubella serology; diagnostic value*

Rubella or German measles, is a highly contagious acute viral infection. This disease is usually accompanied by a rash and is generally mild in children or adults. However, if it occurs in pregnant women who lack immunity to rubella, it can be fatal, to the fetus to be born, especially if the infection occurs in the first trimester of pregnancy. Congenital fetal abnormalities due to rubella infection are known as congenital rubella syndrome (CRS). The syndrome is a collection of disorders known as the CRS triad: heart defects, congenital cataracts, and hearing loss in the form of severe sensorineural deafness. This syndrome can also appear in the form of other congenital disabilities.[1-4]

Congenital rubella syndrome occurred in more than 105,000 infants worldwide in 2010. The *World Health Organization* (WHO) estimated that 238,000 children are born with CRS before the vaccination's era and that there are 100,000 new cases yearly, especially in developing countries.[5,6] Since the rubella

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immunization program in the US began in 1969, the incidence of rubella has reportedly decreased yearly and was eliminated in 2004.[7] In Australia, the incidence of CRS was 1 per 2,000 live births during prevaccination in 2015.[8,9] The rubella infection incidence in Indonesia in 2016 was the highest in the world, and in 2017 the incidence was 5.6 per 100,000 live births.[10-12]

A definite diagnosis of CRS is made based on the clinical manifestations of CRS and the serological test results for rubella.[10,11] However, not all hospitals in Indonesia have the technology to perform serological rubella tests to establish a diagnosis of CRS. The clinical manifestations of group A are hearing loss, congenital heart disease, congenital cataracts, and pigmentary retinopathy, while those of group B are purpura, splenomegaly, microcephaly, developmental delay, meningoencephalitis, radiolucent bone abnormalities, and jaundice that appears within 24 hours of birth.[5]

Immunization can prevent rubella infection and CRS. Based on data from reports on immunization coverage, especially for measles and rubella, in Aceh Province in 2022, not a single city/district in Aceh has achieved the daily target (79.4%) of measles-rubella immunization. The lower the immunization coverage, the greater the risk of an outbreak disease occurrence. To prevent rubella infection in pregnant women, immunization coverage should be increased by 80% to form herd immunity. Thus, immunization is the best and most effective preventive measure to prevent CRS.[3,13-18]

In the study, we aimed to evaluate the diagnostic value of group A and group B clinical manifestations compared to rubella serology results in the diagnosis of CRS at Dr. Zainoel Abidin's Regional General Hospital (ZARGH), Banda Aceh. The results of this study are expected to be the basis for early diagnosis of CRS in children aged 0-12 months, especially in health facilities that lack the facilities to perform serological rubella examinations, such as ZARGH. This study was conducted with the hope that CRS can be more early diagnosed, especially in health facilities with limited resources.

Methods

This observational study with a cross-sectional approach was done to determine the diagnostic value of group A and B clinical manifestations of CRS compared to serological rubella results. Rubella serology testing was performed retrospectively in patients who met the clinical manifestations of CRS. IgM rubella serology test was for baby < 6 month and IgG and IgM serology test indicated for babies aged 6-12 months carried out from blood samples taken at ZARGH and sent to measles rubella national laboratory. The inclusion criteria for this study were children less than 12 months old with clinical manifestations of A and B groups of CRS, met the diagnostic criteria for clinical CRS suspicion and have complete data on the form of CRS 1. Meanwhile, patients who did not have complete data were excluded from this study. Then, the obtained data was subjected to statistical analysis to obtain value of sensitivity, specificity, PPV, NPV, accuracy, PLR, and NLR. The study was conducted in the medical record unit of Dr. Zainoel Abidin's Regional General Hospital, Banda Aceh. Subjects were included by total sampling. Secondary data were obtained from medical records of patients with suspected or clinical CRS at Dr. Zainoel Abidin's Regional General Hospital, Banda Aceh.

This study was approved by the Ethics Committee of the Medical Faculty of Syiah Kuala University/Dr. Zainoel Abidin's Regional General Hospital, Banda Aceh.

Results

Subjects were 126 infants that met clinical manifestations of A and B groups of CRS (aged 0-12 months), comprised of 65 (51.5%) males and 61 (48.4%) females. A total of 80 (63.5%) subjects had normal birth weight, with 98 (77.8%) subjects born full term. Of the 126 subjects, 20 (15.9%) had positive serological results and 106 (84.1%) subjects had negative serological results. The number of subjects aged <6 months was 89 (70.6%), and only 1 (0.8%) subject died (**Table 1**).

The basic characteristics of subjects' mothers are shown in **Table 2**. Multigravida status was noted in 93 (73.8%) mothers, while 96 (76.2%) were pregnant and/or gave birth at the ideal age (20-35 years). Symptoms and history of travel during pregnancy were experienced by 79 (62.7%) mothers of subjects.

The distribution of group A clinical manifestations is shown in **Table 3**. All subjects had one or more signs and symptoms of group A (126; 100%). The most common type of group A abnormality found was congenital heart disease (84; 66.6%), followed by congenital cataracts in 33 (27.0%) subjects, and sensory neural hearing loss in 6 (4.8%) subjects.

Subjects who experienced group B signs and symptoms are shown in **Table 4**, of which the most common were microcephaly in 41 (50.0%) cases, followed by developmental delay in 28 (34.2%) subjects.

Tables 5 show that the clinical manifestations of group A in suspected CRS patients had 100% sensitivity, 0% specificity, 15.9% positive predictive value (PPV), 0% negative predictive value (NPV), 15.8% accuracy value, as well as a positive likelihood ratio (PLR) of 1 and a negative likelihood ratio (NLR) of 0.

The cross-tabulation test analysis of group B clinical manifestations and serological results are shown in **Table 6**, which revealed 75% sensitivity, 36.8% specificity, 18.3% PPV, 88.6% NPV, 34.9% accuracy, 0.4 PLR, and 0.6 NLR.

The diagnostic value of group A and group B clinical manifestations and serological results are shown in **Table 7**. The diagnostic values for groups A and/or B manifestations and serology, with 100% sensitivity 6.6% specificity, 16.8% PPV, 100% NPV, 29.3% accuracy, 1.1 PLR, and 0 NLR.

Table 1. Basic characteristics of subjects

Characteristics	(N=126)
Gender, n (%)	
Male	65 (51.6)
Female	61 (48.4)
Birth weight, n (%)	
Normal (2,500-3,999 grams)	80 (63.5)
Low birth weight (<2,500 grams)	43 (34.1)
Macrosomia (>4,000 grams)	3 (2.4)
Age, n (%)	
≤ 6 months	89 (70.6)
> 6 months	37 (29.4)
Baby's condition, n (%)	
Alive	125 (90.2)
Died	1 (0.8)
Serology results, n (%)	
Positive	20 15.9)
Negative	106 (84.1)

Table 2. Characteristics of subjects' mothers

Characteristics	(N=126)
Gestational age, n (%)	
Premature (< 37 weeks)	25 (19.8)
Mature (37-40 weeks)	98 (77.8)
Postmature (>40 weeks)	3 (2.4)
Parity, n (%)	
Primigravida	33 (26.2)
Multigravida	93 (73.8)
Maternal age at pregnancy, n (%)	
<20 years	1 (0.8)
20-35 years	96 (76.2)
>35 years	29 (23.0)
Symptoms and/or history of travel during pregnancy,* n (%)	
Yes	79 (62.7)
No	47 (37.3)

*(conjunctivitis, runny nose, cough, fever, maculopapular rash, lymphadenitis, arthralgia/arthritis, history of contact with people with rash)

Table 3. Frequency distribution of signs and symptoms in Group A (N=126)

Variables	1 sign and symptom	2 signs and symptoms	Total, n (%)
Congenital heart disease	78	6	84 (66.6)
Congenital cataracts	30	4	34 (27.0)
Congenital glaucoma	2	0	2 (1.6)
Pigmentary retinopathy	0	0	0
Sensorineural hearing loss	6	0	6 (4.8)

Table 4. Frequency distribution of signs and symptoms in Group B

Variables, n (%)	(N=82)
Purpura	2 (2.4)
Microcephaly	41 (50.0)
Meningoencephalitis	6 (7.3)
Jaundice within 24 hours of birth	2 (2.4)
Splenomegaly	3 (3.7)
Developmental delay	28 (34.2)
Radiolucent bone disease	0

Table 5. Clinical manifestations of Group A on serology results

Clinical manifestations	Serology		Total
	Positive	Negative	
Yes	20	106	126
No	0	0	0
Total	20	106	126

Table 6. Clinical manifestations of Group B on serology results

Clinical manifestations	Serology		Total
	Positive	Negative	
Yes	15	67	82
No	5	39	44
Total	20	106	126

Table 7. Clinical manifestations of Groups A and B on serology results

Clinical manifestations	Serology		Total
	Positive	Negative	
Yes	20	99	119
No	0	7	7
Total	20	106	126

Discussion

This study is the first in Aceh to look at the diagnostic value of group A, group B, and groups A and B clinical manifestations compared to the gold standard of rubella serology results to diagnose CRS. A collection of clinical manifestations, divided into two major groups, namely, A and B, is indispensable for diagnosing CRS. At birth, the serum of infants with CRS contains maternal rubella-specific immunoglobulin G (IgG) and their own IgG and IgM antibodies. However, maternal rubella-specific IgG can also be found in normal infants born to mothers who are immune to rubella. Therefore, rubella-specific IgM is used to diagnose congenital rubella infection in infants.[13] In infants with CRS, rubella-specific IgM can be detected in almost 100% of those aged 0-5 months, about 60% of those aged 6-12 months, and 40% of those aged 12-18 months. Immunoglobulin M (IgM) is rarely detected when the child is aged 18 months or more.[13]

In 2019-2021, there were 126 cases suspect CRS, of whom 20 (15.9%) had positive rubella serology results. Of those with positive serology, the most common group A clinical manifestations were congenital heart disease (55%), congenital cataracts (45%), as well as hearing loss and congenital glaucoma in 1 (5%) case of each. The most common group B clinical manifestations in those with positive serological results were developmental delay (60%), microcephaly (55%), and splenomegaly in (10%). Our results were in alignment with the CRS surveillance report of the *Republic of Indonesia Ministry of Health*, 2022, with a reported 585 suspected CRS cases, a definite CRS classification of 8 cases, clinical CRS of 62 cases, and 508 eliminated. The number of cases in 2022 decreased from those in 2021, when suspected CRS totaled 916 cases, with 29 cases of definite CRS classification, 200 cases of clinical CRS, and 687 eliminated. The most common group A clinical manifestations in infants with positive serological results in 2022 were congenital heart disease (4; 50%), followed by congenital cataracts (2; 25%), and hearing loss in (1; 13%). In 2021, congenital heart disease was the most common group A clinical manifestation in CRS cases with positive serological results (14; 48%), followed by hearing loss (7; 24%), and congenital cataracts (2; 7%).[19] Our findings also align with a previous study in Yogyakarta.[10] Of those with positive serology, the most common group A clinical manifestations were congenital heart disease, (10; 83.3%), followed by hearing loss (9; 75%), and congenital cataracts (8; 66.7%). As for the group B clinical manifestations in those with positive serological results in our study, most cases had developmental delays.[11] In 2021, a study found that 229 patients had suspected CRS for five years (2015-2020). A total of 47 (20.7%) infants had positive rubella serology results, mostly

in the 1-5 month age grouping. The group A clinical manifestations in those with positive serological results were congenital heart disease (43; 91.4%).[11] In contrast, the surveillance survey report of the *Republic of Indonesia Ministry of Health* in 2022 noted the group B clinical manifestations of microcephaly, followed by development delay and jaundice.[12]

Group A clinical manifestations had an excellent sensitivity of 100%, while group B had sensitivity of 75%. Moreover, when the clinical manifestations of group A were added to those of group B, the sensitivity increased to 100%. This excellent sensitivity value suggests that the clinical manifestations of group A plus group B might be suitable as a screening tool because they can "catch" many patients with suspected CRS. The low PPVs in group A (15.9%), group B (18.3%), and group A plus group B (16.8%) is still acceptable for a diagnostic study with screening purposes, because this diagnostic will likely have many false positive results. The NPVs in group A (0%), group B (88.6%), and group A plus group B (100%) indicated that they effectively excluded patients without CRS. However, the group A clinical manifestations had PLR of 1 (<10) and NLR of 0 (<0.1), while group B clinical manifestations had PLR of 0.4 (<10) and NLR 0.6 (>0.1), and group A plus group B clinical manifestations had PLR of 1.1 (<10) and NLR 0 (<0.1), which, overall, had a good diagnostic value for diagnosing CRS.

This study had several limitations. We used secondary data from the patients' medical record, so some data were missing. There was also lack of knowledge and information among healthcare staff about CRS, thus affecting the selection of suspected CRS cases.

In conclusion, group A plus group B clinical manifestations have a sensitivity value of 100%. This excellent sensitivity value suggests that these clinical manifestations would be suitable as screening tools for patients with suspected CRS.

Conflict of interest

None declared.

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