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## Seropositivity of Anti-Rubella Antibodies as A Marker for Rubella Infection in Infants at High Risk of Congenital Deafness

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### ABSTRACT

Hearing loss in newborns or congenital deafness can be caused by the development of several parts of the auditory system. Congenital deafness is often associated with infections, such as Toxoplasmosis, Rubella, Cytomegalovirus (CMV), and Herpes (TORCH). Deafness is very difficult to be early detected. Therefore, simple but fast methods are needed. Early detection is based on the Newborn Hearing Screening (NHS) program. Otoacoustic Emission (OAE) and Automated Auditory Brainstem Response (AABR) checks are raw materials for early detection. Congenital deafness often occurs with pregnancy infections with viruses such as Rubella. Rubella infection during pregnancy, especially during the first trimester, often causes Congenital Rubella Syndrome (CRS). Rubella infection often occurs with other causes, such as Toxoplasma, CMV, and Herpes. A Serological test can be used as one of the diagnostics of this infection. This study used single Rubella IgG and IgM antibodies and double antibodies test as a marker for the infection. The authors wanted to correlate the serological examination of this infection with the auditory function. Rubella infection was detected with single serological anti-Rubella IgG and IgM and double multiple Rubella and TORCH serological tests. Also, the auditory function was assessed using the OAE and AABR test in this research. The result showed 35 (77.7%) patients with positive Rubella serological tests among 45 NICU patients at Dr. Soetomo Hospital. There were number of patients was 12 (34.2%) patients with a single positive serological test and 23 (65.7%) patients with positive multiple TORCH serological tests. The number of patients with Rubella negative infection was 10 (22.2%). There were 11 (31.4%) patients of positive Rubella infections with positive hearing loss and 24 (68.6%) patients with negative hearing loss. From the results of the study, 35 patients were at high risk of disturbance and the statistical analysis showed that there were no significant serological differences in Rubella positive with hearing loss ( $p=0.087$ ). Hearing loss in NICU infants has a high risk of factors causing Rubella infection and other related causes. In most Rubella positive serological tests IgG was found, which can be due to maternal factors. Serology tests need to be repeated for confirmation under the surveillance program. How to follow-up the patients and define the next laboratory test after six months remain a great challenge. The efforts need to be strengthened in surveillance programs.

**Keywords:** Automated auditory brainstem response, anti-Rubella, DOAE, hearing loss, serological tests

### INTRODUCTION

Hearing loss in newborns or congenital deafness can be caused by failure to develop one or more parts of the auditory system or the cessation of the development process at a certain stage. In addition, there are also several factors can cause degeneration of the mechanism of hearing development.<sup>1</sup> Congenital deafness is often associated with pregnancy infections with viruses such as Toxoplasmosis, Rubella, Cytomegalovirus (CMV), and Herpes (TORCH).<sup>2</sup> The US Preventive Services Task Force (USPSTF) in 2002 reported that the prevalence of deafness in neonates in the Neonatal Intensive Care Unit (NICU) and infants with specific

risk factors was 10-20 times greater than the prevalence of deafness in the normal neonatal population.<sup>3</sup>

Hearing screening is very important because it is known there are 50% of newborns with risk factors for hearing loss from birth. Hearing loss in infants can be early detected with the Newborn Hearing Screening (NHS) program. Oto Acoustic Emission (OAE) and Automated Auditory Brainstem Response (AABR) are the gold standards for early detection of hearing loss in infants.<sup>4</sup> The American Academy of Pediatrics Task Force on Newborn and Infant Hearing 1999 reported that there was 1-3 bilateral deafness in every 1000 live births and 2-4 bilateral deafness in every 1000 infants with NICU care in the

United States (US). Another observation was carried out in Bali Sanglah Hospital Denpasar from February 2005 to February 2006. This study showed OAE examination results in 61 (81.3%) and 4 (5.3%) patients who passed from a total of 75 patients. Screening accuracy showed that OAE sensitivity varied between 80% to 98%, depending on the type of technology used and deafness. Brainstem Evoked Response Audiometry (BERA) had 90% sensitivity and 80% specificity, while Automated Auditory Brainstem Response (AABR) had 99.96% sensitivity and 98.7% specificity.<sup>4</sup> Furthermore, from the BERA examination, normal results were obtained in 8 (10.67%) patients and various degrees of deafness, such as mild deafness, severe deafness, and very severe deafness in the right and left ears were 13 (17.3%) and 16 (21.3%), 19 (25.3%) and 20 (26.6%) patients, and 4 (5.33%) and 1 (1.33%) patients, respectively. Severe deafness in both right and left ears was mostly found, in 22 (29.3%) patients.<sup>5</sup>

Congenital deafness is often associated with pregnancy infections with viruses such as Rubella. Rubella is a disease caused by the togavirus from the genus Rubivirus. In general, children may not experience severe constitutional symptoms, but adults may experience prodromal 1-5 days of mild fever, headache, malaise, mild runny nose, and arthralgia or arthritis which can occur up to 70% of an adult female with Rubella. If there is a Rubella infection during pregnancy, especially during the first trimester, fetal infections often cause Congenital Rubella Syndrome (CRS), abortion, and severe birth defects. The most common congenital defects are sensorineural deafness, cataracts, heart disease, and physical and mental retardation.<sup>6</sup> Rubella is often associated with other infections, such as namely Toxoplasma, CMV, and Herpes. Toxoplasma infection with mild symptoms around 10-20% is similar to influenza symptoms, characterized by fatigue, malaise, fever, and generally, does not cause problems.<sup>7</sup>

Rubella infection which can cause hearing loss with the organ degeneration process of Corti, the process of adhesion between membrane Corti and Reissner, causing partial or complete stria atrophy and degeneration of nerve elements. Primary infection in a pregnant female is characterized by seroconversion of IgV CMV antibodies during pregnancy or CMV IgG and IgM together during pregnancy. Recurrent infections are characterized by CMV antibodies in the phase before conception. In primary infection, the transmission of infection to the baby is 40%. Anti-CMV IgG in pregnant female does

not provide protection to the baby; thus, congenital abnormalities may occur.<sup>7</sup> Herpes simplex infection in infants occurs when the mother is infected at the end of pregnancy. This is because newly infected mothers do not have antibodies to the virus, resulting in no protection for the baby at birth. Additionally, new Herpes infections are often active, with a higher chance of that the virus presence in the birth canal during child birth. This virus can be in a latent form, radiating through sensory nerve fibers and dwelling in the autonomic nervous system and causing chronic damage to the CNS.<sup>7</sup>

Considering that the a forementioned impacts cause a real disruption and give a big burden if there is a teratogenic effect, an easy and in expensive prevention effort needs to be developed in the future, by conducting an immunization program. As a basis for the implementation of the program, it is necessary to investigate the number of the incidence of Rubella infection in infants with multiple TORCH infections at the NICU Neonatology division of the Department of Child Health at Dr. Soetomo Hospital, Surabaya.

## METHODS

The research sample was taken with consecutive sampling from July to December 2014. The ethical clearance was granted by KEPK, Dr. Soetomo General Hospital, Surabaya no. 467/Panke. KKE/XI/ 2014. This research was observational analytic with a cross-sectional design. The study was conducted at the Audiology Hospital Dr. Soetomo Hospital. Infants were referred from the NICU and tested for Rubella infection by the serological test of Rubella IgG and IgM antibodies. There were 35 infants with serologically positive Rubella and 10 infants with serologically negative Rubella. The researcher examines the hearing function test on 35 infants. There hearing tests with OAE and AABR examinations using the Maico MB11 or German made BERAPHONE devices in 2011. This examination can only use a limited stimulus intensity, which is 30-40 dB. AABR does not require interpretation from audiologists; AABR interprets responses to certain intensity as pass and refers criteria.

## RESULT AND DISCUSSION

The study found 35 patients with Rubella seropositivity among total on 45 patients. Thirty-five patients were at high risk of hearing loss. From the results of statistical analysis, no significant

differences were found between Rubella seropositivity and hearing loss.

The examination of high-risk babies was carried out in the NICU room of Dr. Soetomo Hospital, Surabaya. The serological test was carried out in the NICU treatment room after the condition was stable. After the serological test results were obtained, all subjects were categorized as positive anti-Rubella seropositive with or without multiple TORCH infections. Furthermore, if it was possible for auditory screening examinations using OAE and BERAPHONE, the results were recorded and analyzed with the following data. Distribution of age and serologic tests can be seen in Table 1.

In this study, 21 (46.67%) infants with the highest age group (<1 month) were found (Table 2).

**Table 1.** Distribution of patient age

Age (month)	Total
<1	21 (46.67%)
1-<3	12 (26.67%)
3-<6	9 (20%)
≥ 6	3 (6.66%)
Total	45 (100 %)

**Table 2.** Distribution of serologic test

Serologic Test of Rubella	Total
Rubella	12 (34.2%)
Rubella + Toxo	3 (8.5%)
Rubella + CMV	7 (20%)
Rubella+CMV+Toxoplasma	13 (37.1%)
Total	35 (100%)

As seen in Table 2, the results of serological tests of Rubella IgG and IgM antibodies showed Rubella seropositivity in 35 (77.7%) patients, consisting of 12 (26.6%) patients with single positive Rubella and 23 (51.1%) patients with double-positive TORCH Rubella.

From Table 3, screening with DPOAE showed 26 (61.9%) passed results and (19.0%) referral results among patients <1 month age. Also, screening with AABR showed 29 (64.44%) passed results and 12 (26.66%) referral results.

From these data, it was shown that there were 11 (31.4%) positive Rubella infections with positive hearing loss and 24 (68.6%) with negative hearing loss. In addition, 10 (22.2%) patients with negative Rubella infection with normal hearing were found (Tabel 4).

From the data in Table 5, there were 35 patients with a risk of hearing loss.

**Table 3.** Results of hearing screening with DPOAE and AABR

Age (month)	DPOAE		AABR	
	Pass	Refer	Pass	Refer
<1	10	11	13	7
1-<3	7	5	9	2
3-<6	8	1	4	3
≥ 6	1	1	3	0
Total	26(61.9%)	8 (19.0%)	29 (64.44%)	12 (26.66%)

**Table 4.** Rubella infection with hearing loss

		Hearing		Total
		Refer	Pass	
Rubella infection	Positive	11 (31.4%)	24 (68.6%)	35 (77.7%)
	Negative	0	10 (22.2%)	10 (22.2%)
Total		11 (31.4%)	34(75.5%)	45 (100%)

**Table 5.** Estimated risk of hearing loss

	95% Confidence Interval		
	Value	Lower	Upper
Odds ratio for Rubella infection + (single/multiple)	.278	.062	1.250
For cohort hearing=Refer	.435	.166	1.135
For cohort hearing=Pass	1.565	.854	2.867
N of valid cases	35		

**Table 6.** Serologic test of single and multiple Rubella infections

Hearing Screening	Serologic Test of Single Rubella Infection	Serologic Test of Multiple Infection	Total
	Positive	Positive	
Pass	6 (17.1%)	5 (14.2%)	24 (68.5%)
Refer	6 (17.1%)	18 (51.4%)	11 (31.4%)
Total	12 (34.2%)	23 (65.7%)	35 (100%)

As shown in Table 6, there were 12 (26.6%) patients with hearing loss with single Rubella infection and 23 (65.7%) patients with double Rubella infection.

Hearing loss which is early detected and intervened at the age of fewer than six months will show a better manifestation. In addition to their better speech ability, children without hearing loss also have the better ability at school and productivity in the work environment compared to children with hearing loss which are slowly detected and intervened at the age of more than six months.<sup>8,9</sup> In this study, infant Rubella IgG and IgM antibody were not regularly examined. Table 1 in result section, it seemed that early detection has been carried out well, and screening was mostly carried out at the age of less than one month in 21 babies (46.66%) and up to the age of three months in 12 babies (26.67%) The largest age range was more than six months because in that age range parents are usually aware of the delayed speech and worry about it. This condition will make parents take their go doctor. Earlier detection and intervention will have an impact in the better results for children with hearing loss. Developed countries such as the United States have universally performed hearing screening programs in all newborns and become a routine test for detecting infants with hearing loss. The results of hearing referral results were obtained in 8 (19%) and AABR OAE examinations, 12 (26.66%). This was in accordance with the sensitivity for AABR examination which is better than OAE which can detect interference with the cochlea to the outer hair cells, while AABR can reach the auditory nerve to the brain stem.<sup>10,11</sup>

In this study, there were 35 infants (77.7%) with Rubella seropositivity from a total of 45 infants and hearing function was tested on them. OAE and Automated Brainstem Evoked Response Audiometry (AABR) were examined in March to December 2015. This study showed 8 (61.9%) referral results on patients and 26 (61.9%) pass results; while the results of examination with AABR showed 29 (64.44%) pass results and 12 (26.6%) referral results. Automated brainstem evoked response audiometry provided higher results than DOAE in this study. The gold

standard for this examination is AABR because AABR provides the best results with the highest sensitivity and specificity with AUC values close to 100% (0.97). The hearing screening results were obtained from one test and/or both, which suggested that it was necessary to follow-up with the next examination.

During the period of infection, there will be viremia which lasts between day 5 and 7 after exposure to the Rubella virus. The incubation period of the Rubella virus ranges between 14-21 days. Period of transmission is 1 week before and 4 days after the onset of the rash. The absence of typical symptoms in Rubella infection makes clinical diagnosis often difficult to make. For this reason, a definitive diagnosis by serological examination such as an increase in antibody titers 4 times in hemagglutination inhibition test (HAIR) or the detection of IgM antibodies specific to Rubella is used.<sup>12</sup> In this study, a serological test was carried out during treatment in the NICU room and samples were sent to Clinical Pathology. The results showed seropositivity to anti-Rubella IgG.<sup>13</sup> Seropositivity to anti-Rubella antibody was found in 35 (77.7%) infants with multiple infections. The most obtained is seropositivity to anti-Rubella IgG was mostly found in this study. Statistical analysis showed no significant difference between Rubella seropositivity and hearing loss ( $p=0.087$ ). The relationship between serological Rubella positive and multiple infections with hearing loss, high-risk infants with congenital deafness and serological antibodies positive for Rubella double infection during 2014, there were 6 infants with referral hearing screening results, represented by one of the referring results of OAE or AABR. Rubella infection was with positive laboratory results. Several factors cause congenital deafness, such as Rubella, Cytomegalovirus, Toxoplasma, Herpes, and other dual infections which will provide information as a basis for prevention.<sup>14</sup> Efforts to control can be done by launching the Rubella immunization program and procuring vaccines that are suitable for local isolates in accordance with the findings.<sup>15</sup> Prevention is the most important as the implementation of hearing screening for newborn babies to decrease the

incidences of congenital deafness by 2030 according to the mission of the sound hearing.

## CONCLUSION AND SUGGESTION

Hearing loss in NICU infants are at high-risk of Rubella infection and other related causes. This is supported by the multiple causes of TORCH. Seropositivity of anti-Rubella IgG was mostly found, probably due to maternal factors. Serology tests must be repeated, despite constraints in surveillance. For this purpose, inter-collaboration of several departments must be strengthened in surveillance programs.

Prevention is important to reduce the incidence of congenital deafness. The program of Infection control must be implemented at the NICU for patients and health workers in their environment. Deafness can be prevented with an early detection program (New Born Hearing Screening Program).

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