Correlation between specific rubella immunoglobulin G (Ig G) and response evoked brainstem audiometry examination on confirmed congenital rubella syndrome (CRS) patients

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ABSTRACT

Congenital rubella syndrome (CRS) is a health problem that can cause deaf child. Its diagnosis is based on clinical manifestation, specific rubella Immunoglobulin M (IgM) and IgG examination. The aim of this study was to evaluate the correlation between the specific rubella IgG level and the brainstem evoked response audiometry wave V. This was a cross sectional study involving congenital rubella syndrome (CRS) child patients at Dr. Sardjito General Hospital, Yogyakarta from 2011 to December 2016. The inclusion criteria were 1) aged less than 24 months; 2) wave V of brainstem evoked response audiometry examination has been identified. The exclusion criteria were 1) the patient's parents refused to participate and 2) incomplete data. Based on α: 5%, β: 20% and coefficient correlation estimation 0.04, minimal sample size were 47 subjects. All of subjects was underwent specific rubella IgG examination. Statistical analysis by using Spearman`s correlation test. Wave V at the level <25 dB were found in 2 patients (4.3%), 26-40 dB results in 3 (6.4%) patients, 41-60 dB in 1 (2.1%) patient, 61-80dB was found in 9 (19.1%) patients and > 81 db in 32 (68.1%) patients. A significant positive linear correlation between IgG levels (4-400 IU/mL) and wave V of brainstem evoked response audiometry was reported ($p<0.05$; $r = 0.432$). In conclusion, there is a positive correlation between specific rubella IgG level and brainstem evoked response audiometry test results.

ABSTRAK

Sindrom rubella kongenital adalah masalah kesehatan yang dapat menyebabkan tuli pada anak. Diagnosisnya didasarkan manifestasi klinis, pemeriksaan rubella immunoglobulin M (IgM) dan IgG spesifik. Tujuan penelitian ini adalah menentukan korelasi antara kadar IgG spesifik rubella dan tanggapan bangkit otak respon audiometri gelombang V pada pasien sindrom rubella kongenital. Penelitian ini dengan rancangan potong lintang ini melibatkan anak sindrom rubella kongenital di Rumah Sakit Umum Pusat Dr. Sardjito Yogyakarta dari tahun 2011 hingga Desember 2016. Kriteria inklusi adalah 1) pasien berusia kurang dari 24 bulan dan 2) gelombang V brainstem evoked response audiometry telah diidentifikasi. Kriteria eksklusi adalah 1) orang tua pasien menolak berpartisipasi dalam penelitian dan 2) data yang tidak lengkap. Berdasarkan nilai α: 5%, β: 20% dan estimasi koefisien korelasi 0,04, ukuran sampel minimal adalah 47 pasien. Semua pasien menjalani tes IgG spesifik rubela. Analisis statistik dengan menggunakan uji korelasi Spearman. Total sampel 47 pasien. gelombang V pada tingkat <25 dB ditemukan pada 2 pasien (4,3%), hasil 26-40 dB pada 3 (6,4%) pasien, 41-60 dB pada 1 (2,1%) pasien, 61-80dB ditemukan pada 9 (19,1%) pasien dan> 81 db pada 32 (68,1%) pasien. Hasil uji linearitas antara kadar

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IgG (4-400 IU/mL) dan gelombang V diperoleh hubungan linear positif yang signifikan (p <0,05; r: 0,432). Berdasarkan hasil penelitian ini dapat disimpulkan terdapat hubungan positif antara kadar IgG spesifik rubella dan tanggapan bangkit otak respon audiometri.

Keywords: congenital rubella syndrome - immunoglobulin G - hearing threshold - brainstem evoked response - audiometry examination.

INTRODUCTION

Congenital rubella syndrome (CRS) is a combination of several conditions of physical abnormality that develop in infants as a result of maternal rubella virus infection that spreading to the fetus. If infection occurs at 0-12 weeks of gestation, there is an 80-90% risk of fetal infection. The most common congenital defects include sensorineural deafness, eye damage such as cataracts, cardiovascular disorders and mental retardation. Rubella virus is transmitted through the respiration via droplet issued by someone infected with rubella virus. After exposure to droplet, the virus will experience replication in the nasopharynx and lymph nodes.[1,2]

Fetal organ damage is caused by various factors, for example by cell damage due to cell division of the rubella virus which causes focally dispersed necrosis areas in the chorionic villi epithelium and capillary endothelial cells. Cells infected with the rubella virus have a short lifespan, the infected fetus's organs have lower cell numbers than healthy fetuses. This is because during a young pregnancy the fetal defense mechanism is immature.[1-3]

Congenital rubella syndrome has one of the major defects of neurosensory hearing loss, caused by histopathologic hearing loss in maternal rubella infections in the fetus, indicating that temporal bone changes in the cochleosaccular whereas utricles, semicircular canals, and ganglion are usually unaffected. The tectorial membrane was found rolled up and floated inside the sulcus.[4]

The mechanism of the immune response in CRS is slightly different from that of other viral infections, when the infant serum is born with CRS containing a specific rubella-carrying immunoglobulin G (IgG) that is brought from the mother in addition to the immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies formed from his own body.[5,6]

Brainstem evoked response audiometry (BERA) is an objective electrophysiological method for assessing the auditory process from the auditory nerve to the brainstem. Indications of examination of BERA include newborns with risk factors for hearing loss as in CRS it is useful to know the development of retrocochlear hearing pathway due to damage that occurs in cochlear.[7-10] The aim of this study was to evaluate the correlation relationship between the levels of specific rubella IgG with the results of the wave V level BERA examination.

MATERIALS AND METHODS

Study design

The design of the study was cross sectional on the study were all CRS (P.35.0) pediatric patients

Time and location

The study took place in the Department of Perinatology and Department of Otorhinolaryngology Head and Neck Surgery at Dr. Sardjito General Hospital Yogyakarta, which included routine physical ear nose, and throat exam, OAE (otoacoustic emission), and BERA. The study was conducted in a period of December 2011 to December 2016.

Population and samples

Study population CRS pediatric patients.

All study population was performed Ig G and wave V level BERA examinations. The inclusion criteria were 1) aged less than 24 months. 2) the intensity of sound emerged wave V of BERA inspection has been identified. The exclusion criteria were 1) the patient's parents refused to participate in this study, 2) incomplete data.

Samples

The sample size were calculated using sample size formulation for case control study. Based on α: 5%, β: 20% and coefficient correlation estimation 0.4, minimal sample size were 47 subjects. The research variable was specific rubella Ig G concentration and the result of the wave V level BERA examination.

Statistical analysis

Data were presented as mean (minimum-maximum) and then tested using Spearman correlation test and the result was plotted the pair of data samples on Cartesian diagram called scatterplot. A $p < 0.05$ was considered significance.

RESULTS

The characteristics of patients consisted of age at diagnosed, sex, congenital heart disease, congenital cataracts, wave V level BERA result are presented in TABLE 1. A total patientwas involved edNo significantly difference in sex distribution was observed (p=0.382). The youngest patient who suffer from RCS at the time of diagnosis was < 1 month, whereas the oldest subject was 23 months with the mean age of 7.02 months. patientonly free from the clinical symptomsForty-five (95.7%) suffered from the hearing loss and only 2 (4.3%) did not suffer from the hearing loss. and only 17 (36.2%) did not suffer from the .

TABLE 1. Characteristics of the subjects.

Characteristics	n (%)	p
Age [Mean (min-max) months]	7.02 (0 – 23)	
Sex		
• Male	27 (57.4)	0.382
• Female	20 (42.6)	
Congenital heart disease		
• Yes	38 (80.9)	0.001
• No	9 (19.1)	
Cataract		
• Yes	30 (80.9)	0.079
• No	9 (19.1)	
Hearing impairment		
• Yes	45 (95.7)	0.001
• No	2 (4.3)	
Wave V level BERA (db)		
• <25	2	
• 26-40	3	
• 41-60	1	
• 61-80	9	
• > 80	32	
IgG (range level IU/mL)	4-400	

The scatter plot diagram between IgG level and wave V level BERA and its correlation analysis are presented in FIGURE 1 and TABLE 2. Significantly correlation between IgG concentration and wave V level BERA was reported ($r = 0.432$; $p = 0.001$; $n = 94$).

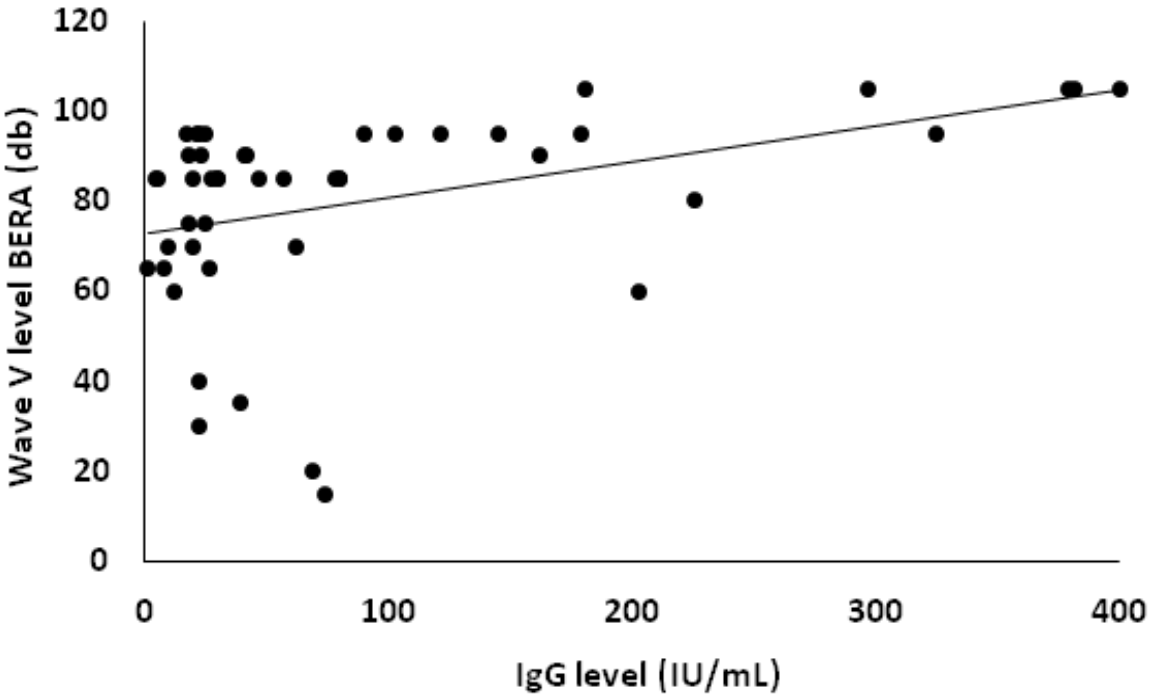

FIGURE 1. Correlation between specific rubella IgG level and wave V level BERA

TABLE 2. Correlation between IgG andwave V level BERA

Level of IgG	Wave V level BERA
Correlation coefficient	0.432*
p	0.001
n	94

*) significant p <0.05; Spearman correlation

DISCUSSION

The mean age of the subjects in this study is different from the previous study which is 8 years old.[11] The subjects in this study were 27 (57.4%) male patients and 20 (42.6%) female patients. However, this difference was not significant. This result is in accordance with previous study that showed there is no difference in the incidence of CRS by sex.[12]

The occurrence of congenital cataract number in this study was not significant (p = 0.079), while the congenital heart disease was significant (p = 0.001) in CRS. In the previous study was found 10-15% cases of congenital cataract and 46% cases of congenital heart disease based on specific serologic examination in the population suffering from CRS.[12]

The condition of hearing loss in the sample of this study found in 45 (95.7%) patients and only 2 (4.3%) patients did not suffer from hearing loss. The incidence of hearing loss in a previous study were 48.5% of all samples which positive serum-specific serologic examinations found. The above is due to the risk of congenital infections and defects recalled during the first 12 weeks of pregnancy and decline after pregnancy over 12 weeks with rare defects in 20 weeks' pregnancy.[1,2]

The immune response mechanism in CRS must be slightly different from that of other viral infections. When a baby serum is born with CRS must contain a specific rubella-carrying IgG that is brought from the mother in addition to the IgM antibodies formed from his own body. This specific maternal rubella IgG can also be found in normal babies born to mothers who have been immune to rubella. Therefore, to diagnose the infection of CRS in infants based on a

specific rubella-specific IgM. In infants with definite CRS, the specific rubella IgM can be detected almost 100% at 0-5 months, 60% at 6-12 months of age and 40% at 12-18 months. The specific IgG of the maternal rubella titer continues to decrease and is rarely detectable at 6 months of age, when detection of specific rubella IgG is possible from the baby's own immune system.[5]

The CRS includes 3 primary defects i.e. first is neurosensory-type hearing loss, second is a heart disorder including Persistent Ductus Arteriosus (PDA), Ventricular Septal Defect (VSD) and pulmonary stenosis, the third is eye disorders including cataract and glaucoma. The above can be explained by if rubella infection occurs at 0-12 weeks of maternal pregnancy, then the possibility of 80-90% risk of fetal infection. Histopathologic damage to the hearing organ on maternal infection, showing temporal bone there is a change in cochlea and saccule, in its development if damage occurs in the area, then the hearing path that leads to the brain stem will not develop maximally even degenerate.[1,2,13]

Results wave V level BERA at the level <25 db were found in 2 (4.3%) patients, 26-40 db results in 3 (6.4%) patients, 41-60 db in 1 (2.1%) patient, 61-80 was found in 9 (19.1%) patients and > 81 db in 32 (68.1%) patients. Dewan *et al.*[12] conducted a study on 140 infants tested BERA, 70 normal babies, and 70 infants with various risk factors such as CRS, obtained 44 (31.3%) infants with various risk factors showed abnormal BERA results. In the IgG test, the result showed that 42 patients (89.4%) positive result with titer > 15 IU/mL, while 5 (10.6%) patients negative result with titer <10 IU/mL.[14]

Early detection of hearing loss in this study was already under way. The children with hearing impairment can gain early management, by develop their linguistic and educational abilities as adults. Early detection has begun to wake up, and habilitation can be achieved immediately. Several recent cohort studies and other studies have demonstrated that diagnosis and intervention before 6 months of age can improve the language, speech, cognitive and social skills of children with hearing loss.[15,16]

Correlation test results can be seen significance level, meaning if $p<0.05$ or not significant if $p >0.05$, correlation strength (very weak: 0.000-0.199, weak: 0.200-0.399, medium: 0.400 -0.599, strong: 0.600-0.799 and very strong: 0.800-1.00), as well as direction of relationship between two variables tested (positive direction or negative direction).[16]

Linearity test was also conducted in this research, it was intended to evaluate the relationship between the two research variables in this case the level of IgG and wave V level BERA examination results, whether the relationship was linear or not. Based on linearity test result between variable of IgG level and wave V level BERA examination result, there was a linear relationship between IgG level and wave V level BERA ($p <0.05$). The correlation coefficient value of 0.432 (TABLE 2) has a higher mean of specific rubella IgG, the greater the occurrence of deafness seen based on the BERA result.

CONCLUSION

There is a positive correlation relationship between specific rubella IgG level and wave V level BERA test results. The higher levels of specific rubella IgG, the greater the hearing loss is seen from the wave V level BERA results.

Serologic IgG can help determine the prognosis of hearing loss in patients with surveillance CRS. It is necessary to conduct further study in order to obtain a reference in the patient's management of habilitation with CRS that will improve the quality of life of the patients.

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