Biomedical Journal of Indonesia
Journal Homepage: https://bji-fk.ejournal.unsri.ac.id

Long-Term Growth and Development Monitoring Of Children With Rhesus Hemolytic Disease of The Newborn

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ARTICLE INFO

Keywords:
Hyperbilirubinemia
Rhesus hemolytic
Diseases of the newborn
Kernicterus
Growth and development

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.32539/BJI.v9i2.162

ABSTRACT

Rhesus hemolytic disease of the newborn (RHDN) occurs due to alloimmunization of maternal red blood cells. Complications of RHDN in infants can lead to hyperbilirubinemia, kernicterus, and anemia. In Indonesia, RHDN prevention has not been a common activity so it is very important for pediatricians to recognize early signs of an infant with severe anemia and severe hyperbilirubinemia, to prevent long-term mortality and morbidity. A case with longitudinal observation of long-term growth and development of a child with a history of RHDN has been reported. Throughout the monitoring carried out, the child did not experience serious problems in the medical field but showed disorders or developmental delays that did not improve over time with various therapeutic efforts. Based on a serial monitoring and treatment data that has been carried out on the child, we assumed there has been permanent brain damage caused by hyperbilirubinemia conditions accompanied by co-morbid sepsis. Brain damage is characterized by low DQ values from the beginning, progressive head circumference leads to microcephaly conditions and the presence of brain defects in the form of arachnoid cysts. The management of child development disorders with RHDN to date has not shown encouraging results. Therefore, experts have shifted their focus towards preventive measures, such as intra-uterine fetal transfusion, which has been shown to significantly decrease the occurrence of RHDN-related child development disorders over the past decade.

1. Introduction

The Rhesus hemolytic disease of the newborn (RHDN) occurs due to alloimmunization of maternal red blood cells.[1] The production of maternal antibodies will fight certain antigens from fetal red blood cells, usually Rhesus D (RhD), and will go through the blood circulation of mothers who do not have these antigens. Maternal immunoglobulin (IgG) will pass through the placenta into the circulation, leading to symptoms ranging from mild to severe hemolytic anemia and a hydrops fetalis condition. Complications of RHDN can lead to hyperbilirubinemia, kernicterus, and anemia.[2,3]

RHDN in developed countries is now eradicated. Knowledge about rhesus disease has been known for approximately the last six decades, and its prevention has been known since 40 years ago.[2,4]

In Western countries, 15% of the population is rhesus negative with high serum bilirubin levels in cases of rhesus isoimmunization.[5] RHDN condition is rare in African and Asian populations.[6] The number of rhesus-negative blood owners in Indonesia is 1%.[7]

RHDN prevention in Indonesia has not been a common activity in clinical settings. Hence, it is very important for pediatricians to recognize early signs of an infant with severe anemia and severe hyperbilirubinemia to prevent long-term mortality and morbidity.

Management of RHDN aims to reduce the incidence of severe neonatal hyperbilirubinemia and encephalopathy due to bilirubin.[3,5,8] Prenatal prevention aiming all pregnant women for ABO and rhesus (RhD) groups testing and screening for the presence of iso-immune antibodies.[4] Specifically, by administering intrauterine blood transfusions (IUTs).[2,4] The main postnatal management of RHDN for treating hyperbilirubinemia consists of intensive phototherapy and exchange transfusions.[3,8]

Several postnatal complications of RHDN have been reported, including long-term impacts on child development. Proper management will reduce both short- and long-term morbidity.[5]

This longitudinal case report aims to monitor the growth and development aspects of children suffering from RHDN after Exchange Transfusion as a long-term complication of the disease.

2. Case Presentation Section

Initial Data

A 6-month-old boy came to the growth and development clinic complaining of developmental delays compared to his peers. The patient is still unable to lift his head and social smile; weight is also difficult to gain.

History Of The Disease

Patients born in private hospitals spontaneously per vagina with gestational age 39 weeks, Apgar Score first minute 7 and fifth minute 9, without any trauma during labor, clear amniotic fluid. Birth weight 3500 grams, body length 49cm, and head circumference 35cm. A few hours after the baby is born, jaundice is obtained on the body. Laboratory tests showed an increase in total bilirubin 19.9 mg / dL, direct bilirubin 0.8 mg / dL, and patients received phototherapy. On the third day of treatment, the baby has a fever and poor feeding; antibiotics and intravenous fluid infusions are administrated. Blood type examination in infants and parents of infants shows the blood type of infants AB, mothers AB and father B. Photo therapy continued, and on the fifth day, the patient appeared to be increasingly jaundice, and total serum bilirubin levels 38.83 mg / dL and direct bilirubin 12.78 mg / dL then the baby was referred to a Tertiary Health Facility with a diagnosis of full-term neonate, hyperbilirubinemia and suspicion of sepsis.

The patient's mother was a 30-years-old Arab woman, and the patient's pregnancy was her second. There were no problems during the antenatal period and regular control mothers. There is no history of diabetes mellitus, hypertension, and infection in the mother's previous disease history. No history of taking drugs, herbs, and alcohol. Parental marriage is not consanguinity. The pregnancy and delivery of the first child were not a problem; the first child is currently healthy with a 3-year age difference with the patient.

Initial examination when in the emergency department, on physical examination obtained lethargy patients, with a pulse 150 times/minute, axillary temperature of 36.7°C,and respiratory rateof 60 times/minute. Jaundice from face to toe and pale are found. No signs of hemorrhage. Fontanel anterior is still open and does not bulge. Lung examination, no abnormalities were obtained. A cardio examination showed tachycardia, no murmurs or gallops were obtained. No liver enlargement or splenomegaly was obtained on examination of the extremities, pale, jaundice and warm with a capillary refill time of < 3 seconds.

The results of initial laboratory tests showed hemoglobin (Hb) 8.6 g/dL, hematocrit (Hct) 25.6%, total bilirubin 37.16 mg/dL, direct bilirubin 21.28 mg / dL, alanine transaminase and 13 U/L, aspartate transaminase 44 U/L, albumin 3.31 g/dL, C-reactive protein (CRP) 112.3mg/L.

Based on the history taking, physical examination, and laboratories, the initial diagnosis of this patient is full-term infants, hyperbilirubinemia, and second-degree acute bilirubin encephalopathy. Patients are examined leading to hemolytic disease, work up for hemolytic disease planned for laboratory tests: a Coomb test, reticulocyte count, peripheral blood smears, G6PD (glucose 6-phosphate dehydrogenase deficiency). Initial management of patients received fluid therapy, Intravenous immunoglobulin (IVIg), and exchange transfusion.

Further laboratory tests showed an increased reticulocyte count of 1.7%, positive direct Coombs test, venereal disease reaction level (VDRL) and treponema pallidum haemaglutination assay (TPHA) nonreactive. Examination of the parents' blood type showed AB's mother was rhesus negative; father B was rhesus positive. From the examination results, the patient was diagnosed with full-term infants, hyper-bilirubinemia due to RHDN, acute bilirubin encephalopathy of 2nd degree, and suspected sepsis.

Post-exchange transfusion laboratory examinations, albumin transfusion, and IVIG administration showed a significant decrease in total bilirubin levels of 15.17 mg/dL direct bilirubin 9.2 mg/dL. Hb 12.9 g/dL, Hct 35.9%, leukocytes 10860/µL, platelets 135100/uL, albumin 3.2 g/dL, CRP 1 mg/L. The patient was discharged in good condition and planned for monitoring of growth and development. Growth and development monitoring is necessary to evaluate the complications posed by RHDN.

Genetic Factors / Heredo-constitutional

The patient is the 2nd of 2 children. The patient's mother (age 25) was rhesus negative, who was only discovered when the patient was born and suffered from rhesus incompatibility.

Like most people, the patient's father (age 30) was rhesus positive. When the anamnesis was carried out, the family claimed to have just learned about this rhesus incompatibility disease. A history of similar conditions in the family lineage is denied. The history of consanguinity between the parents is denied. The patient's maternal grandfather is someone with rhesus negative blood type, while the patient's grandmother is rhesus positive blood type.

Observation

At the beginning of the observation period, several patient problems were found, as listed in Table 1.

Table 1. List of problems and plans for solving them at the beginning of the observation period

	Problems	Plans
Growth Aspect	Anthropometric examination using the WHO Z score curve: W/L and W/A are between -2 to -3 SD, L/A, HCA are at -2SD.	- Anthropometric monitoring every six months - CT scan of the head for evaluation of microcephaly and other organic disorders - Nutritional counseling
Developmental Aspect	DENVER II examination at the age of 6 months, there was a delay in 4 basic developmental aspects	- Progress monitoring every six months using DENVER II and CAT-CLAMS - Hearing evaluation with BERA - Counseling on the fulfillment of intensive stimulation of developmental aspects
Social Aspect	The family is still working in the medical and non-medical fields for the recovery of patients.	Accompany and discuss with family about the advantages and disadvantages of non-medical therapies.

Table 2. Growth and development monitoring plan

Observation	1	2	3	6	7	8	9	10	12
Examination									
- BERA	V								
- Brain CT-Scan									V
Growth									
- Ht/BW/HC	V						V		V
Developmental									
- DENVER II	V						V		V
- CAT/CLAMS							V		V

Figure 1. Patient baby S, age six months when coming to Growth and Development Clinic

First Observation (6 m.o)

Patients a 6-month-old came to the growth and development clinic for growth and development evaluation. The patient's general condition seems good. The main complaint of the family is that the child has not been able to raise his head or smile spontaneously.

Growth and development evaluation, the nutritional status of children at that time using the WHO growth curve weight for length, between -2 to -3 SD wasted, weight for age 6 kg between -2 to -3 SD under-weight, length for age 63 cm, between -2 to -3 SD stunted, head circumference for age 41 cm between -2 to -3 SD microcephaly. Nutritional counseling provides breast milk and additional food in milk porridge.

Developmental screening evaluation with DENVER II at six months of age found delays for four aspects of development. Conclusion The patient is suspect of 4 basic developmental aspects.

Evaluation of patient growth and development, planning for examination of hearing tests with BERA (brain stem evoked auditory response), evaluation of brain abnormalities with CT scan of the head. Counseling on stimulation, the patient is six months old, but from 4 basic aspects, the patient's mental age is equivalent to children aged 1-2 months; thus developmental stimulation is given according to children 1-2 months.

Second Observation (9 months old)

The main complaint of the family is that the child is still unable to lift his head has begun to be able to smile spontaneously. From the results of the growth and development evaluation, nutritional status using the WHO growth curve weight for length at -3 SD wasted, weight for age 6.3 kg at -3 SD underweight, length for age 63 cm at -2 SD stunted, head circumference for age 41 cm between -2 to -3 SD microcephaly. Nutritional counseling provides breast milk and additional food in soft rice.

Developmental screening with DENVER II at nine months of age found delays in 4 aspects of development. Conclusion: The patient suspect for four basic developmental aspects. Developmental evaluation using CAT-CLAMS at nine months of age. Measurement results with CAT-CLAMS: CLAMS DQ=36, CAT DQ=21, Fullscale DQ=28, with the conclusion of Mental Retardation.

Hearing test evaluation examination with BERA (brain stem evoked auditory response) and head CT scan is currently not done. Developmental stimulation counseling is given to children with development equivalent to 1-3 months.

Third Observation (12 m.o)

The main complaint of the family, at this time, the child still unable to roll over has begun to be able to smile socially. From the results of the growth and development evaluation, the nutritional status of children at that time using the WHO growth curve weight for length at -3 SD wasted, weight for age 7.1 kg at -3SD under-weight, length for age 70 cm between -2 to -3 SD stunted, head circumference for age 43 cm between -2 to -3 SD, microcephaly. Nutritional counseling provides breast milk and additional food in the form of rice and family meals.

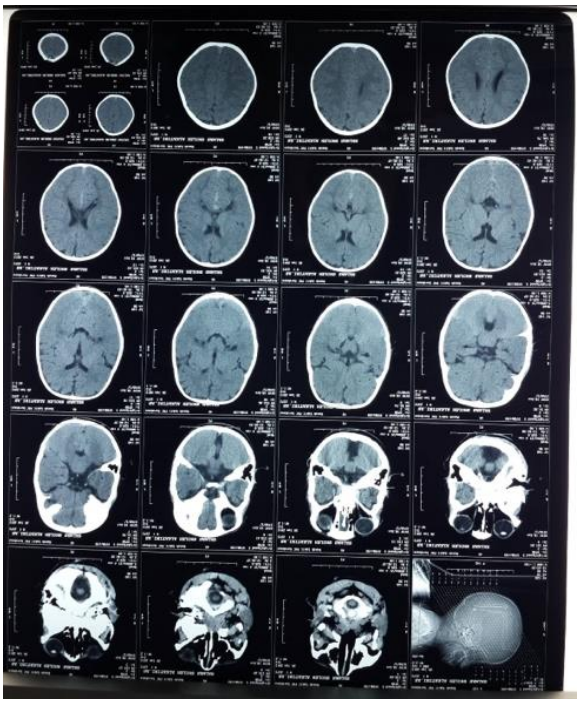

Figure 2. CT Scan of the patient's brain at the age of 12 months, with the results of an arachnoid cyst in the occipital region

Developmental screening with DENVER II at 12 months of age found delays in 4 aspects of development. Conclusion: suspect on four basic aspects of development. BERA (brain stem evoked auditory response) evaluation is still not done. CT Scan of the brain has been done with the results of an arachnoid cyst in the occipital region.

Developmental status verification using CAT-CLAMS at 12 months of age. Measurement results with CAT-CLAMS: CLAMS DQ=38, CAT DQ=24, Full scale DQ=31, with the conclusion of Mental Retardation. We gave counseling to parents to provide developmental stimulation to children with development equivalent to the age of 1-3 months.

3. Discussion

Rhesus hemolytic disease of the newborn (RHDN) generally occurs due to maternal and fetal rhesus antigen incompatibility and its consequences associated with maternal sensitization. Severe hemolytic conditions due to RHDN occur since the fetus in-utero will manifest as progressive anemia and hypoalbuminemia, which causes anasarca edema and heart failure (hydrops fetalis) and can result in fetal death at birth. If it survives at birth, it manifests as jaundice and severe anemia that can develop into acute bilirubin encephalopathy (kern-jaundice) and result in neonatal death. If the child is able to survive, the condition can cause brain damage with all the consequences for long-term growth and development.[5]

The long-term growth and development of children with a history of RHDN varies greatly influenced by various factors. RHDN with very high hyperbilirubinemia without other co-morbid factors is said to have better outcomes than when accompanied by co-morbid factors such as sepsis, premature, low weight, and so on.[9–11]

The study, summarized 28 studies over a period of 30 years from 128 cases of acute-bilirubin encephalopathy (ABE) or kernicterus in term children, showed an association between high bilirubin levels and the occurrence of kernicterus. Although rare, kernicterus has a significant mortality rate (about 10%) and a long-term morbidity rate of about 70%. If not accompanied by other co-morbid factors, hyperbilirubinemia will develop into ABE if the level of TSB (total serum bilirubin) ranges from 22.5-54 mg / dl. When accompanied by sepsis co-morbid factors, the range of TSB levels becomes even wider (4-51 mg / dl).[12,13]

Long-term impact studies show that children with term hyperbilirubinemia accompanied by sepsis have significantly higher global developmental delays. [9–11] In this case, the child is able to survive with good neonatal period care. After neonatal care, children do not experience significant health problems. However, in the observation of long-term growth and development until reaching the age of 12 months, children appear to grow with weight and lenght which are relatively less with the size of head circumference leading to a state of microcephaly. The development of children's abilities also experiences delays in all aspects (global developmental delayed).[5]

Growth and development journey that occur in this child, theoretically seem in line with the predictions of experts such as conditions in some developed countries. As in Denmark and Canada, children with acute bilirubin encephalopathy are 82.4% (95% CI:59.0-93.8%) likely to develop a developmental disorder, and 47.1% (95% CI:26.1-69.0%) will develop cerebral palsy (CP). [5]

Specifically for long-term developmental journey infants with RHDN who experience jaundice, universally the morbidity rate for experiencing various developmental disorders at the age of two years is about 13%. Only about 2% show normal development by age 2. If RHDN cases are not accompanied by acute bilirubin encephalopathy, the normal probability at the age of 2 years reaches 50%.[5]

In the case, this child, developmental monitoring using the milestone achievement scale with Denver II obtained suspect results, with delays in all aspects (gross motor, speech-language, fine motor, and personal social). This global development delay condition begins to appear from the beginning of observation after neonatal care and relatively does not experience significant improvement until the child reaches 12 months.

The use of Denver II as a developmental monitoring tool in patients remains to be further verified, considering Denver II is a screening-level developmental detection tool. Theoretically, the Denver II examination has limited validity, although it has a reasonably high sensitivity value (83%), but the specificity value is relatively low (43%).[14]

Considering the various limitations of monitoring progress using milestone achievement, this patient also carried out verification of developmental monitoring using quantitative scales by Developmental Quotient (DQ) with the Capute Scales method better known as the cognitive adaptive test / clinical linguistic auditory milestone scale (CAT/ CLAMS) instrument.[15]

Developmental quotient measurement values with the CAT/CLAMS method in these patients when they reached the age of 12 months, DQ CAT: 24 DQ CLAMS: 38, and FS DQ: 31 were obtained, with the final conclusion of mental retardation.

The results of DQ assessment in the case of this child at the age of 12 months, theoretically have a sensitivity value of 64% and specificity of 98% when compared to the MDI value of <70 (Table 7).[16,17] So that the possibility that this child in the future will experience CP and/or accompanied by mental retardation is relatively large.

A study by Zhang W, 1995, longitudinally study follow up the long-term development of hyperbilirubinemia children produced evidence that

lower DQ of hyperbilirubinemia children compared to controls began to appear as early as 2 months of age (P = 0.03). There was no significant correlation between high serum bilirubin levels and duration of hyperbilirubinemia and low DQ. So it is recommended that long-term monitoring of the development of children with hyperbilirubinemia should be done for all children regardless of bilirubin levels.[18,19]

In this case child found various conditions, including: full-term child, Hyperbilirubinemia due to RHDN, Acute bilirubin encephalopathy of the 2nd degree, suspicious sepsis, global development delay, high risk of experiencing CP and mental retardation.

Various efforts to monitor and manage long-term development have been carried out, but until the age of 12 months the child has not shown significant developmental progress. This is very likely to be caused by very severe biological factors, in this case there may have been brain damage in various areas. Brain damage that occurs in cases of RHDN does not always appear on CT-Scan or MRI, usually the picture of brain damage will appear subtle. Brain damage caused by high hyperbilirubinemia conditions is generally in the form of a buildup or disposition of bilirubin in certain areas of the brain that can be clearly seen macroscopically only when an autopsy is performed, including: the globus palidus area, hippocampus, lateral ventricular wall, cerebellum and subthalamus nucleus.[20]

In this case there has been permanent brain damage for several reasons: (1) There is a delay in achieving milestones from the beginning of observations, which does not improve significantly until the end of observations; (2) DQ values were very low from the beginning of observation and also did not improve significantly until 12 months of age; (3) Head circumference tends to have a progressive decrease, and (4) Brain defects in the form of arachnoid cysts are found at 12 months of age.

Unfortunately, until now there are no certain criteria that can distinguish child development disorders caused by hyperbilirubinemia with other causes. However, through good child history data, physical examination and laboratory examination, a categorization of high levels of unconjugated bilirubin (UCB) can be made that causes mild, moderate and severe jaundice, which can cause developmental disorders in children.[21] Dysregulation in "programming development" due to high or moderate UCB levels, will affect the function of brain microglia in the long term, so the risk of cognitive impairment in the future.[22]

In general, the prognosis of children in this case in terms of long-term growth and development is not good. In the future children are very at risk for mental retardation in a state of CP, because there has been permanent brain damage. However, various optimization efforts are still needed to guide parents to respond to the child's situation in the future. RHDN in developed countries today has indeed been eradicated. With the improvement in perinatal mortality rates of RHDN children, in the last decade the focus of RHDN child management has begun to shift to various preventive measures for the long-term impact of developmental disorders. One that is widely developed is through prenatal management with intra-uterine fetal transfusion. Intrauterine prenatal transfusions are said to prevent long-term developmental disorders, with about 92% of RHDN children not showing any sensorineural impairment by age 2.[23,24]

4. Conclusion

The management of child development disorders with RHDN to date has not shown encouraging results. Therefore, experts in the last decade have focused more on preventive measures, one of which is intra-uterine fetal transfusion. This action is said to significantly reduce RHDN child development disorders.

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