Neonatal hemolytic disease due to anti-Diegoa antibody: a case report

Yangxi Fu1*, Ying Liu2, Zhenzhen Yang2, Yinhua An2, Jun Su3, Shuli Hu4 and Lingying Luo4

Abstract

Background: The Diegoa antigen commonly occurs in certain Asian and South American Indian populations. In general, hemolysis caused by anti-Diegoa antigen is not severe, and exchange transfusion is rarely needed. Here, we report a neonate with moderate hemolytic disease caused by anti-Diegoa antigen in the Baoji area of China.

Case presentation: A 39-week gestation male newborn of Han nationality was delivered by second cesarean section because of scarred uterus. The newborn’s birth weight was 3700 g with an Apgar score of 9. Four hours after delivery, transcutaneous bilirubin test revealed a level of 17 mg/dl. After 23 hours, the neonate developed anemia and hyperbilirubinemia. Bacterium, virus and other pathogens, as well as tests for arcuate and glucose-6-phosphate dehydrogenase, were all negative. Direct antiglobulin test of the neonate was positive. Diegoa antigens of the baby and his father were positive, while his mother was negative. The newborn was successfully cured with phototherapy and one-dose intravenous injection of human albumin.

Conclusions: It is important to consider and test for the anti-Diegoa antibody in cases of hemolytic disease of the newborn of the Han ethnicities of China.

Keywords: Anti-Diegoa antibody, Neonatal hemolytic disease, Case report

Introduction

The Diego blood group system was first introduced in 1955 by a case of hemolytic disease of the newborn caused by anti-Diegoa antibodies (anti-Dia) [1]. The Diego blood group system is composed of mainly three sets of antithetical antigens: Dia/Dib, Wra/Wrb, and Wu/DISK [1]. Subsequent studies have found that the Diego blood group antibodies (for example, anti-Dia and anti-Dib) can cause hemolytic transfusion reaction (HTR) and hemolytic disease of the fetus and newborns (HDFN or HDN) [2].

The distribution frequency of Dia antigen in different ethnic groups and regions is known to be very different. Genetic study revealed that Dia antigen was relatively common among Asians of Mongoloid origin and South American Indians, as compared with Caucasians and Blacks [3]. Only a few publications reported that Dia was a low-frequency antigen in Europe, such as 0.89% in Berlin [4] and 0.46% in Poland [5]. One study in a South Texas community demonstrated a relatively high frequency (2.6–4%) in previously transfused patients from an area with 20–54% Mexican donors [6]. Another study showed that Dia incompatibility among the southern Thais (0.93%) was lower than among the central Thais (3.49%) [7].

Anti-Dia antigen has been reported as being responsible for moderate to severe HDN [5, 8, 9]; however, it rarely caused a fatal hemolytic transfusion reaction [10]. In this paper, we report a case of moderate HDN caused by Dia antibody. Fortunately, blood transfusion and red blood cell suspension injection were not required.
His parent gave written informed consent for publication. This manuscript adheres to the applicable EQUATOR guideline: CARE checklist.

**Case presentation**

A 39-week gestation male newborn of Han nationality, delivered by second cesarean section because of scarred uterus, was born in the sixth hospital of the Baoji area. The newborn’s birth weight was 3700 g with an Apgar score of 9. His mother had no history of blood transfusion. This was her second pregnancy; her first child was a healthy 7-year-old girl. Routine prenatal examination for irregular antibodies had never been performed during her second pregnancy. The condition of the baby stabilized, and there were no findings of fetal distress. Four hours after birth, the baby was found to have obvious jaundice and transcutaneous bilirubin test reached a level of 17 mg/dl in the sixth hospital of the Baoji area. Then he was immediately sent to the neonatal intensive care unit of our hospital for further evaluation and monitoring, and the transcutaneous bilirubin level was 16.5 mg/dl on admission and first treated with intensive phototherapy for 16 hours. Laboratory results were as follows (23 hours after birth): red blood cell (RBC) 3.3 × 10¹² cells/L, white blood cell count 15.73 × 10⁹ cells/L, hemoglobin 12.9 g/L, hematocrit 36%, platelet count 223 × 10⁹/L; liver function test showed total bilirubin 13.3 mg/dl, and unconjugated bilirubin 12.6 mg/dl. C-reactive protein (CRP) was 63.5 mg/L, procalcitonin was 6.2 ng/ml, and interleukin-6 was 299.8 pg/ml. The following tests were all negative: blood culture, urinalysis, and stool (microscopic examination), cerebrospinal fluid routine, cerebrospinal fluid culture and biochemistry, tests for blood cytomegalovirus, herpes simplex virus, and other pathogens, as well as tests for arcuate and glucose-6-phosphate dehydrogenase (G-6-PD).

The newborn and his mother were typed as blood group A, RhD+. The subtypes of Rh blood group were classified C, c, D, E, and e. Free test and diffusion test were negative. The neonate’s red cells reacted positively (1+) in the direct antiglobulin test (DAT) including (IgG + C3d) polyclonal antibody; however, the anti-IgG test had a positive result, while anti-C3d test was negative. The irregular antibodies of the mother by microcolumn gel technology combined with anti-human globulin (IgG + C3d) were positive (IgG 1+, C3d–). Because the mother did not receive blood transfusion and gamma globulin, we speculated that the anti-IgG might be against a rare blood group system. No antibodies against red blood group system were identified in tests using commercial antibody screening blood cell (Rh-hr, Kidd, MNSs, Duffy, Lewis, P). Anti-Dia was finally identified in the neonate’s serum from tests with a commercial panel of red blood cells (spectrum cells including Rh-hr, Kidd, MNSs, Duffy, Diego, Kell, Lewis, P, DO, Yt) from the Shanghai Blood Biotechnology Company, China. To confirm the anti-Dia, blood samples of the newborn and his parents were sent to Shanghai Blood Center and further performed using a monoclonal anti-Dia and monoclonal anti-Dib standard serum, respectively. Thus, father and child were positive for Diα antigen, while mother was negative for Diα antigen. Diβ antigen was negative for all of them.

The neonate was successfully treated with intensive phototherapy for 120 hours over 10 days, and received intravenous injection of 70 ml human albumin injection. The bilirubin level dropped to 8.2 mg/dl within a few days of treatment, and therefore, no blood exchange transfusion was needed because the hemolysis was not aggravated. The infant was in a healthy state and was discharged home with the following laboratory findings: RBC 3.02 × 10¹² cells/L; hemoglobin 111 g/L; hematocrit 34.1%.

**Discussion**

In the past, ABO and Rh incompatibility generally accounted for HDN. With the determination of blood group antibody titer and the use of anti-D immunoglobulin in pregnant women, fatal and severe HDN has been dramatically reduced in recent years. Owing to prenatal and postnatal maternal serum irregular antibody screening for pregnant women, the special antibodies to rare RBC surface antigens, such as Diα and Diβ, were subsequently identified. These antibodies played an important role in rare and severe HDN.

In our case, the mother had not been screened for irregular antibodies during the pregnancy. Unfortunately, postnatally, the irregular antibodies of the mother’s serum were positive, and the neonate had clinical signs of HDN with positive DAT. In the present study, the mother was negative for Diα antigen, but the baby and father were positive. Anti-Dia antibody is also pregnancy-induced [5, 11] and is detectable from birth [3, 12]. We speculated anti-Dia antibody formation during this pregnancy, and its level increased, crossed the placental barrier, and entered fetal circulation. Quantity of fetal RBC cells attached to anti-Dia antibodies might be enough to lead to postnatal clinical signs of HDN and cause positive DAT.

In general, hemolytic disease of the newborn induced by anti-Dia is not severe; however, some cases may be serious enough to require exchange transfusion [11, 12]. The baby demonstrated moderate hemolysis and hyperbilirubinemia due to anti-Dia, similarly to cases reported previously [8, 13, 14]. Nevertheless, our findings are apparently contradictory to several other reports.
and Arends, for example, could not find a case of HDN in 40 families tested, in which fathers were Di⁺⁺, mothers
Di⁻, and children Di⁺⁺ [15]. Zeljka Hundric-Haspl et al.
reported a neonate who had no clinical signs of HDN
despite positive DAT, and the pre- and postnatal screen-
ing tests of the mother were also all negative; however,
anemia was diagnosed 3 weeks later, and it was caused by
anti-Diego derived during pregnancy, which led to low-
level Di RBC antigen [16]. Moreover, a few examples of
agglutinins of anti-Di specificity have been reported in
individuals with no known RBC exposure [1], the reasons
for which remain unknown.

It is well known that the Di antigen is usually associ-
ated with Mongolian populations in Asia. In Japan, how-
ever, there is no significant difference in the prevalence
among Mongolians, Zhuangs, Chinese–Koreans, and
Japanese as reported by Komatsu et al. [17]. In China,
the Di⁺ antigen is usually found among the Korean and
Zhuang nationalities [18]. Overall, these findings confirm
that the Di⁺ antigen occurs largely among people of
Mongolian origin. In China, in particular, the Mongolians
are distributed mainly over Inner Mongolia, Gansu,
Xinjiang, Shaanxi, and northeast China [18]. The Baoji
area is located in Shaanxi Province, which belongs to the
northwest region of the mainland, and the Mongolian
people are scattered here. However, the baby in this case
study was of a Han nationality instead of a minority, and
so were his parents, who were also local residents. This
suggests that the Di⁺ antigen may be present in diverse
populations.

To the best of our knowledge, the present study may be
the first report of this case in Shaanxi Province, China.
Although antibodies to Di⁺ antigen are not the main
cause of hemolytic disease of newborns in the area, such
antibodies may lead to severe hemolytic reactions. When
encountering hemolytic disease of the newborn caused
by low-frequency antigen-antibody, it is necessary to
consider the role of anti-Di⁺. It is also recommended that
the screening for Di⁺ antibodies be included in routine
prenatal examinations.

Conclusion
It is important to consider the role of an anti-Di⁺ anti-
body in cases of hemolytic disease of the newborn in the
Han populations in China. It is also recommended that
antibody screenings include anti-Di⁺ screening for all
pregnant women and neonates in order to prevent early
complications of hemolytic disease of the newborn and
potentially harmful outcomes of transfusion therapy.

Abbreviations
Di⁺: Diego⁺; G-6-PD: Glucose-6-phosphate dehydrogenase; DAT: Direct anti-
globulin test; HTR: Hemolytic transfusion reaction; HDFN or HDN: Hemolytic
disease of the fetus and newborns; RBC: Red blood cell; CRP: C-reactive protein.

Acknowledgments
We acknowledge the kind assistance of the patient, the parents, and the staff
involved in the study, conducted in the Department of Blood Transfusion and
Neonatology of Baoji Maternity and Child Health Care Hospital, Children’s
Hospital of Baoji, Affiliated Hospital of Shaanxi University of Chinese Medicine.

Author contributions
YWZ conceived the conception and design, as well as analysis and interpreta-
tion of the results, and writing and revision of the paper. ZZY performed the
experiments. YL and HYA helped in the analysis and/or interpretation of the
test results. JS contributed to the revision of the manuscript. LYL and SLH
provided kind assistance in the study. All authors read and approved the final
manuscript.

Funding
No funding was obtained for this study.

Availability of data and materials
Not applicable.

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient’s legal guardian for
publication of this case report and any accompanying images. A copy of the
written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Department of Respiratory Medicine, Baoji Maternity and Child Health Care
Hospital, Children’s Hospital of Baoji, Affiliated Hospital of Shaanxi University
of Chinese Medicine, Baoji 721000, Shaanxi, China. 2 Department of Blood
Transfusion, Baoji Maternity and Child Health Care Hospital, Children’s Hospi-
tal of Baoji, Affiliated Hospital of Shaanxi University of Chinese Medicine,
Baoji 721000, Shaanxi, China. 3 Department of Neonatology, Zhuhai Hospital
of Integrated Traditional Chinese and Western Medicine, The Second Peo-
ples Hospital of Zhuhai, Zhuhai 519020, Guangdong, China. 4 Department
of Neonatology, Baoji Maternity and Child Health Care Hospital, Children’s
Hospital of Baoji, Affiliated Hospital of Shaanxi University of Chinese Medicine,
Baoji 721000, Shaanxi, China.

Received: 7 June 2022   Accepted: 30 June 2022
Published online: 13 July 2022

References
1. Figueroa D. The Diego blood group system: a review. Immunohematol-
ogy. 2013;29(2):73–81.
2. Wei CT, Al-Hassan FM, Naim N, Knight A, Joshi SR. Prevalence of Diego
blood group antigen and the antibody in three ethnic population groups
in Klang valley of Malaysia. Asian J Transfus Sci. 2013;7(1):26–8.
3. Layrisse M, Arends T. The Diego blood factor distribution: genetic, clinical
and anthropological significance. Bibl Haematol. 1958;7:114–6.
4. Heuft HG, Zeiler T, Zingern J, Eckstein R. Sporadic occurrence of Diego
A antigens and antibodies in Berlin. Infusionsther Transfusionsmed. 1993;20(1–2):23–5.
5. Kusniez-Aleksa G, Bochenek S. Haemolytic disease of the newborn
due to anti-Di⁺ and incidence of the Di⁺⁺ antigen in Poland. Vox Sang.
1992;62(2):124–6.
6. Thompson C. Diego(a) antigen frequency and anti-Diego(a) frequency in
a South Texas community. Clin Lab Sci. 2006;19(4):203–5.
7. Chesor M, Mitundee S, Nathalang S, Thattanon P, Intharanut K, Tobunluepop P, Nathalang O. DI* A and DI* B allele frequencies among southern Thai blood donors. Indian J Hematol Blood Transfus. 2018;34(3):506–9.
8. Jethava A, Olivares E, Shariatmadar S. A case of hemolytic disease of the newborn due to Di(a) antibody. Case Rep Pediatr. 2015;2015: 897803.
9. Ting JY, Ma ES, Wong KY. A case of severe haemolytic disease of the newborn due to anti-Di(a) antibody. Hong Kong Med J. 2004;10(5):347–9.
10. Hinckley ME, Huestis DW. Case report. An immediate hemolytic transfusion reaction apparently caused by anti-Di(a). Rev Fr Transfus Immunohematol. 1979;22(5):581–5.
11. de Lima LMA, Berthier ME, Sad WE, DiNapoli J, Johnson CL, Marsh WL. Characterization of an anti-Di(a) antibody causing hemolytic disease in a newborn infant. Transfusion. 1982;22(3):246–7.
12. Lee SM, Im SJ, Park SE, Lee EY, Kim HH. A case of severe hemolytic disease of the newborn due to anti-Di(a) antibody. Korean J Lab Med. 2007;27(3):373–6.
13. Monestier M, Rigal D, Meyer F, Juron-Dupraz F, Baboin-Jaubert M, Marseglia GL. Hemolytic disease of newborn infants caused by anti-Diego antibodies. Arch Fr Pediatr. 1984;41(9):641–3.
14. Goto M, Sano T, Kubo H, Maeda Y, Maeda T. A case of hemolytic disease of the newborn due to anti-Di(a) antibody. Nihon Sanka Fujinka Gakkai Zasshi. 1987;39(2):323–6.
15. Layrisse M, Arends T. The Diego system; steps in the investigation of a new blood group system; further studies. Blood. 1957;12(2):115–22.
16. Hundric-Haspil Z, Balen-Marunlic S, Tomasic-Susanj E, Tomisic M, Vujaklija-Stipanovic K. Anti-Diego a red blood cell alloantibody as a possible cause of anemia in a 3-week-old infant. Arch Med Res. 2003;34(2):149–51.
17. Komatsu F, Hasegawa K, Yanagisawa Y, Kawabata T, Kaneko Y, Watanabe S, Miyagi S, Sakuma M, Kagawa Y, Kajiwara M. Prevalence of Diego blood group Di(a) antigen in Mongolians: comparison with that in Japanese. Transfus Apher Sci. 2004;30(2):119–24.
18. Yuan YD, Du RF, Chen LZ, Xu JJ, Cui MY, Wang YF, Li SZ, Goedde HW, Bennkman HG, Kriese L, et al. Distribution of eight blood-group systems and ABH secretion in Mongolian, Korean, and Zhuang nationalities in China. Ann Hum Biol. 1984;11(5):377–88.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.