WWJMRD 2023; 9(05): 10-14
www.wwjmrd.com
International Journal
Peer Reviewed Journal
Refereed Journal
Indexed Journal
Impact Factor SJIF 2017: 5.182 2018: 5.51, (ISI) 2020-2021: 1.361
E-ISSN: 2454-6615

Ahmed J. Al Farsi
Neonatal-Perinatal fellow at Hamad Medical Corporation (HMC), Qatar. Senior specialist Pediatrician at Ministry of Health, Oman.

Abdellatif Abdelwahab
Assistant Professor of Clinical Pediatrics Weill Cornell Medical College-Q, Sr Consultant Neonatologist at Women's wellness and Research Center, HMC, Doha Qatar.

Hamdy A. Ali
Assistant Professor of Clinical Pediatrics at Qatar University, Consultant Neonatologist at Women's wellness and Research Center, HMC, Doha Qatar.

Correspondence:
Ahmed J. Al Farsi
Neonatal-Perinatal fellow at Hamad Medical Corporation (HMC), Qatar. Senior specialist Pediatrician at Ministry of Health, Oman.

Severe Neonatal Anemia Due to Feto-maternal Hemorrhage, The Lowest Cord Hemoglobin Values Probably Ever Reported in the Neonatal Literature. Case report

Ahmed J. Al Farsi, Abdellatif Abdelwahab, Hamdy A. Ali

Abstract
Feto-maternal hemorrhage (FMH) is a transfusion of fetal blood into mother circulation resulting in anemia in the newborn. The rate of massive FMH (a volume of 80-150 mL) is about 1: 5,000 births. [(1)] Symptoms of FMH are nonspecific, and mostly it presented as reduced fetal movements and changes in cardiotocography (CTG). Kleihaurer-Betke test is the standard for FMH diagnosis. In this article we are presenting a late preterm noanate with severely low Hemoglobin 1.6 g/dl at birth, attributed to FMH. As per the best knowledge of the team, this could be the lowest cord hemoglobin values probably ever reported in the neonatal literature.

Keywords: Kleihauer–Betke test; neonatal anemia; fetomaternal hemorrhage; reduced fetal movements.

Introduction

The case

History

A late preterm, 35 weeks and 5 days of gestation baby boy born for a mother who is 31 years old gravida 2 para 1 with no significant medical or surgical past history. The delivery achieved via an emergency lower segment cesarean section (LSCS) due to reduced fetal movements noted by the mother for the previous 2 days and non-reassuring non-reassuring cardiotocography (CTG) subsequently. Antenatally, the mother was followed up in regular visits, Group B Streptococcus (GBS) screening was negative, last antenatal ultrasonography was done when the gestation was 35 weeks (ie; 5 days back) and reported as a normal in all parameters including amniotic fluid and doppler waves. Just 2 days prior to delivery, the mother noted that the fetus movements were decreased both in frequency and intensity. Maternal concern taken seriously, and Ultra sonography (US) evaluation was conducted result was re-assuring that evening. However, the next day, mother concerned more regarding fetal movement and visited the heath institute again with the same complain; reduced fetal movement, so another evaluation was done which revealed a non-reassuring CTG. The fetus was delivered urgently.

Delivery and resuscitation details

The neonate born limp, apnic and extremely pale; "white paper-like" in one of the medical records. APGAR Score recorded as 2, 5 and 6 at 1, 5, and 10 minutes respectively. Endotracheal intubation and mechanical ventilation were initiated for poor respiratory efforts. But no cardiac compression nor inotropic medications actually needed. Arterial cord blood gas showed a picture of metabolic acidosis (Ph: 7.02, pCo2 46, BE: -24.6, HCO3: 6.3 and high lactate; 21). The first Hemoglobin (Hb) reading was 1.6 grams per deciliter (g/dl) in the arterial cord blood gas, then the newborn venous Hb recorded as 2.3 g/dl in first hour (Figure1) in Complete Blood Count (CBC) result, hence first Packed Red Blood Cell (P-RBC) transfusion was given urgently while the newborn still in the Operation Theater (OT).

Of note, last mother CBC prior to surgery showed relatively normal maternal Hb of 13.5 g/dl.

WBC	* H 36.8
RBC	L 0.6
Hgb	* C 2.3
Hct	L 7.8
MCV	H 130.0
MCH	H 38.3
MCHC	L 29.5
RDW-CV	H 22.6
Platelet	To follow
MPV	11.0

Fig. 1: The first CBC showing low Hb 2.3 g/dl.

Assessment and management

conducted simultaneously. The baby admitted to Neonatal Intensive Care Units (NICU) for respiratory support with mechanical ventilation, to augment the hemoglobin with multiple (P-RBC) transfusions, and to initiate therapeutic hypothermia for hypoxic ischemic encephalopathy (HIE).

Investigation

CBC: Hb 2.3 g/dl (critically low), RBC 0.6 x10^6/uL (low), Hct 7.8% (low), reticulocytes rate 5.3% and absolute reticulocyte number was 121.1 x10^3/uL (normal). There was no ABO incompatibility as both the mother and her baby have (A positive) blood group. Direct antigen test or coombs test was negative and glucose-6-phosphate dehydrogenase (G6PD) enzyme level was normal. Blood smear film showed insignificant result. Bilirubin was slightly high but not to the level of Phototherapy. Platelet however found low in last couple CBCs, reached minimum of 65 x10^3/uL (low) at 3rd day of life. Of note, the initial CBC in first 1 hour of life showed normal platelets count of 102 x10^3/uL, hence the team thought that the low platelets level could be iatrogenic due to multiple P-RBC transfusions [2] and the thrombocytopenia was treated conservatively. Coagulation profile was normal. Newborn screening for metabolic and genetic disorders showed normal result.

Management of anemia

The neonate received serial blood transfusion as follow; at about 20 minutes of life the baby received 15mls of uncross matched group O negative P-RBC within 30 minutes, followed by another similar dose but given slightly slower; within 1 hour, to avoid cardiac and circulatory overload complications. Next, at age of 3 hours, he received the third dose (group A this time according to his blood group), given similar volume (ie; 15 mls) within 2 hours. Finally, at about 7 hours of age, he was transfused with the fourth P-RBC within 4 hours. In the second day of life, the baby received 15ml/kg of group A P-RBC over 4 hours. The practice of blood transfusion given to the neonate in term of volume and rate was based on the team senior colleague's decision and agreement as there was no specific protocol in such scenario at the time of reporting this case. Furosemide has been used in some of the transfusions to manage the overload concern. The Hb has improved from 2.6 g/dl to 6 g/dl at day 1 of life and then to 9.6 g/dl at the 2nd day of life, to 12 g/dl at 3rd day of life and to 11 g/dl just before discharge at the 11th day of life (Figure 2).

General Hematology	WBC	RBC	Hgb	Hct	MCV
14/12/2022 13:33 AST	L 5.9	4.3	11.3	33.8	78.4
11/08/2022 04:07 AST	6.9	L 3.8	L 11.0	L 32.3	L 85.0
07/08/2022 04:04 AST	L 5.1	L 3.7	L 10.7	L 31.3	L 85.3
04/08/2022 05:13 AST	L 5.6	4.4	L 12.9	L 35.3	L 80.4
03/08/2022 04:32 AST	L 5.0	L 4.1	L 12.4	L 32.5	L 79.9
02/08/2022 04:18 AST	12.6	L 2.8	* C 8.2	L 22.3	L 80.5
01/08/2022 20:18 AST	20.5	L 3.2	L 9.6	L 26.7	L 83.2
01/08/2022 14:20 AST	* H 29.1	L 2.3	* C (c) 6.9	L 19.8	L 86.5
01/08/2022 09:15 AST	* H 36.8	L 0.6	* C 2.3	L 7.8	H 130.0

Fig. 2: Hemoglobin level is increasing in response to management.

Other treatments included 72 hours of therapeutic hypothermia for Hypoxic ischemic encephalopathy (HIE). This was started at age 4 hours of life, after hemodynamic stabilization and ensuring safe level of Hb before starting as the therapeutic hypothermia could carry risk of bleeding and hemostasis disturbance. [3] The team aimed to rise the Hb to a safe level as well as the platelets count, before 6 hours of age, not to lose the window of initiating therapeutic hypothermia. [4] Coagulation profile was stable and didn't change significantly throughout the treatment, the course of treatment went smoothly without significant complications. Magnetic Resonance Imaging (MRI) done in first week of life and no abnormalities detected. Deranged renal and liver functions noted upon admission, and was managed conservatory with the use of special TPN components (HepatAmine™) which thought to help in liver diseases. [5] Mechanical **ventilation** received for total of 30 hours, initial 6 hours of life, then re-intubated again in day 3 possibly due to shallow breathing secondary to morphine used as analgesic for cooling therapy. Chest X ray excluded

any lung pathology. Initial Echocardiography showed small size cardiac shadow indicating volume depletion in the circulation which improved with followed up Echocardiography. Sepsis as a non-specific etiology had been considered, first line antibiotics initiated empirically, the septic screen revealed negative blood culture and low both C- reactive protein and procalcitonin. As a result, the antibiotics were stopped after 5 days. A dose of bicarbonate correction as baby had metabolic acidosis with high lactate and bicarbonate at the first presentation. The neonate discharged home in a good condition, feeding orally, breathing in ease in room air, with follow-up appointments with the neonatology high risk clinic, neurodevelopmental and hematology teams.

Hunting for a cause: Mother blood group is A+ as well as the neonate. there was no solid laboratory evidence suggesting ongoing hemolysis (DAT was Negative, retics initially couldn't be analyzed in lab due to low Hb, subsequently found ranging between 3-7% in following serial CBC, Bilirubin was within normal accepted ranges, lactate dehydrogenase (LDH) was not done as well as haptoglobin. Blood smear not reported back as well as G6PD enzyme level. However, Kleihauer–Betke test was conducted it came positive for fetal hemoglobin in the maternal circulation for 7.5%, which is equal to 375ml of baby blood volume (Figure 3). As a holistic approach, TORCH, sepsis and metabolic disorders has been rolled out, hematology team involved onboard, and other hematology investigations revealed insignificant results in regards of coagulation, but the hemoglobinopathy was unable to be assessed properly due to multiple early transfusions. Genetic test collected and set for investigation which found to be normal later on.

Lab View	01/08/2022 10:25 AST
Special Hematology	
Kleihauer-Betke	A Positive
Fetal Cells %	7.5
Fetal Maternal Hemorrage	375.0

Fig. 3: Kleihauer–Betke test result showing fetal maternal hemorrhage.

Discussion

Patients are not following text books, a well-known said in the medical school; our patient is an example, who has more than one "problems list". He has a neonatal anemia needed blood transfusion, cardiopulmonary collapse needed partial resuscitation, and hypoxic ischemic encephalopathy necessitated cooling therapy. In such scenario, the decision making in regards of management is quite challenging because each measure used to treat one pathology, might itself cause undesired effect on the other pathology! for example, Our patient had hypoxia due to low Hb which fit the criteria of offering him therapeutic hypothermia, however in the other hand he had sever anemia which needed multiple blood transfusion, and augmenting the Hb is a priority as cooling therapy itself might carry risk of bleeding and hemostasis disturbance. [3] An additional challenge is that the cooling therapy window of treatment is available only up to 6 hours of life and after that probably not indicated. [4] The lack of clear consensus on the rate and volume of PRBC transfusion and the target Hb in such acute cases receiving massive transfusion is another gray area lacking high evidence level in literature. [6] Thrombocytopenia was another finding in this case which could be for several reasons; Firstly, up to 30% of neonates with HIE develop thrombocytopenia. [7] Secondly, the effect of therapeutic hypothermia on platelet function. A defective platelet plug formation occurs during therapeutic hypothermia of neonates. [8] Additional cause in our patient can be due the dilutional effect of multiple transfusions, its estimated that red blood cell transfusions decreased the platelet count to an extent two and one-half times greater than that of colloid infusions. [2]

From previous literature, the lowest hemoglobin values reported in pediatric age group were 1.1 g/dl in a 20-months-old boy infant from and 1.2 g/dl in a 6-months-old girl infant. [9] However, our patient could probably, to the best of our knowledge, be the lowest ever reported cord hemoglobin (1.6 g/dl) among the neonatal age group. A previously recorded value in a newborn was 3.6 g/dl in a term neonate delivered emergently due to massive feto-maternal hemorrhage. [10]

For systematic approach, neonatal anemia can be due to one of three main mechanisms; Blood loss, increased RBC destruction, reduced RBC production, ordered from most to the least common. First, blood loss, including obstetrical causes like placental abruption, placenta previa, trauma, anomalous placental vessels rupture, Feto-maternal hemorrhage, Feto-placental transfusion due to positioning of infant above level of placenta after delivery, cord occlusion, twin-twin transfusion, internal hemorrhage such as intracranial hemorrhage, subgaleal hemorrhage, cephalohematoma, adrenal hemorrhage, subcapsular hematoma of liver or ruptured viscus. Iatrogenic blood loss can occur secondary to sampling of blood for laboratory tests.Then, increase in RBC destruction which can be due to hereditary RBC disorders including RBC Enzyme defects (e.g., G6PD deficiency) or RBC membrane defects (e.g., hereditary spherocytosis) or Hemoglobinopathies (e.g., α-thalassemia) or destruction due to immune hemolysis including Rh incompatibility, ABO incompatibility, Minor blood group incompatibility (e.g., Kell, Duffy) or hemangiomas (Karabakh Merritt syndrome). Hemolysis can occur due to acquired causes like like infection, vitamin E deficiency or drugs. Finally, reduced RBC production which includes the anemia of prematurity due to transient deficiency of erythropoietin, aplastic or hypoplastic anemia (e.g., Diamond-Blackfan), bone marrow suppression (e.g., with Rubella or Parvovirus B19 infection) and nutritional anemia (e.g., iron deficiency).

Table1: Average Hemoglobin, Hematocrit and Reticulocytes for different gestational ages
The table cited from University of California Children Hospital-Nursery manual.

Table. Average hematological values for term and preterm infants.

Gestation (weeks)	Hct (%)	Hgb (g/dL)	Retic (%)
37-40	53	16.8	3-7
32	47	15.0	3-10
28	45	14.5	5-10
26-30	41	13.4	—

Kleihauer Betke (KB) test result was positive in the mother labs, which eventually indicate some degree of feto-maternal hemorrhage. KB test is a blood test used during pregnancy to screen maternal blood for the presence of fetal red blood cells. It is mainly used to assess the severity of a feto-maternal hemorrhage (FMH). The idea of the test is based on the fact that baby RBCs are generally rich in hemoglobin F, and hemoglobin F is resistant to acid. A blood sample from the mother is made into a smear on a glass slide, then the slide is flooded with acid. Maternal hemoglobin (presumably hemoglobin A as in most adults) dissolves away and the fetal hemoglobin F remains intact. Then, the slide is washed, stained, and read. The fetal RBCs appear bright red, while the maternal RBCs are pale because they have lost their hemoglobin (Figure 4). The technologist counts 2000 cells, and the percentage of fetal cells is used to predict the percentage of fetal red blood cells in the maternal circulation. This value is then used to calculate the total amount of fetal blood in the mother's circulation. Other methods less commonly used to detect fetal RBC in maternal circulation are flow cytometry and liquid chromatography. [11]

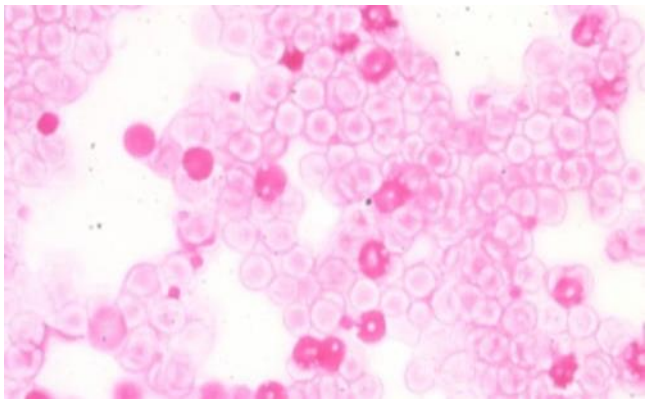

Fig. 4: KB test showing fetal RBC are intensely red while maternal RBC looks pale due to lack of their hemoglobin,
The figure cited from Blood Bank Guy website

FMH can occurs due to several reasons; traumatic or obstetric complications to pregnancy, or due to invasive prenatal procedures like amniocentesis or chorionic villus sampling (CVS). [12] ABO or Rh incompatibility is another reason. None of the previously mentioned reasons are found in our case. Although minor groups incompatibility was not tested and if present it can cause some degree of bleeding, probably not to the extent that out baby had. [13,14] FMH can occur at any time during pregnancy. Clinical signs are nonspecific and unpredictable, and sadly, massive acute bleeding can cause fetal death. Hydrops, abnormal fetal heart rate, and decreased fetal movement can be signs of massive but non-lethal or chronic intermittent acute bleeding, causing large cumulative blood loss over time. Reduced or absent fetal movements are the most common symptom of massive FMH. Usually, the mother is asymptomatic, but occasionally symptoms appear and might suggest typical transfusion reaction (fever, chills, nausea).

When the transfused volume equals or exceeds 20 mL/kg, massive feto-maternal hemorrhage may lead to severe prenatal or neonatal complications. [16] Our patient discharge home healthy, with Hb 13.3 g/dl (See Figure 2). He has no neurodevelopmental sequalae in follow-up.

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