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TITLE PAGE

Title:

Prenatal management of fetal anemia due to pyruvate kinase deficiency: A case report

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Authors' contribution

EM, PM, BL, FD, SP, and AM were responsible for the patient's medical follow-up throughout the pregnancy, including obstetrical management, ultrasound examinations, biologic workup

of the mother, fetus and newborn, and intrauterine transfusions. JMJ and GL provided supervision and mentorship. MSL, PM, BL and EM reported the data. MSL and EM drafted the manuscript. JMJ, PM, SP, BL, FD, AM and GL critically revised the manuscript. Each author made a significant contribution in reviewing the manuscript drafting or revision and accepts accountability for the overall work. All authors approved the final version of the report.

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Fetal transfusion for PK deficiency

Abstract

BACKGROUND: Pyruvate Kinase (PK) deficiency is the most common enzyme defect of glycolysis, leading to congenital hemolytic anemia, which can occur during the neonatal period.

STUDY DESIGN AND METHODS: We report the prenatal management of fetal anemia related to PK deficiency in a family with a severe proband.

RESULTS: The couple had a first child born with hydrops, whose PK deficiency was diagnosed at 18 months of life. He was treated with allogeneic bone marrow transplantation. The second child was free from disease. For the third pregnancy, the amniocentesis revealed a PK deficiency. Weekly ultrasound monitoring of the middle cerebral artery velocity allowed the detection of severe fetal anemia. Two intrauterine red blood cell transfusions (IUTs) were performed, raising the fetal hemoglobin from 6.6 to 14.5 g/dL at 28 weeks' gestation and from 8.9 to 15.3 g/dL at 31 weeks. A hematopoietic stem cell allograft was discussed prenatally but not chosen, as it would not have significantly changed the perinatal prognosis. The patient delivered a 2730g girl at 37 weeks, with a hemoglobin of 13.6 g/dL. The child presented with neonatal jaundice treated with phototherapy and received postnatal transfusions.

DISCUSSION: When a proband is identified in a family, fetal investigation is warranted, to set up third trimester ultrasound surveillance and perinatal management. In case of fetal severe anemia of unknown etiology, the workup on fetal blood sampling before IUT should comprise the search for erythrocytes enzymopathies, such as PK deficiency. IUTs allow safer full-term delivery in cases with PK deficiency.

Keywords: Pyruvate Kinase deficiency, congenital haemolytic anaemia, prenatal diagnosis, intrauterine transfusion, pregnancy, haematopoietic stem cell transplantation

Main document

Introduction

Pyruvate Kinase (PK) deficiency is the most frequent enzyme defect of the glycolytic pathway and the most common cause of chronic hereditary non-spherocytic hemolytic anemia. [1,2] This disease has a worldwide geographical distribution with an estimated prevalence ranging between 1 and 5 per 100,000 in the Caucasian population. [3] Erythrocyte PK deficiency is inherited in an autosomal recessive pattern and is caused by homozygous or compound heterozygous mutations. [4] The degree of anemia is variable, ranging from fully compensated hemolysis diagnosed in adulthood to severe fetal anemia complicated by neonatal death. [4,5] Treatment is mainly based on blood transfusion and, in severe cases, splenectomy. Recent consensus guidelines on the diagnosis of PK deficiency recommend diagnostic confirmation with genetic testing. [1] Thus, prenatal diagnosis of PK deficiency is currently performed in families with index cases with severe anemias. We comprehensively describe the case of a family, whose third child was found to have PK deficiency which led to two intrauterine transfusions (IUTs).

Case presentation

The mother was 26 years old, of Algerian origin, gravida 3 para 2, with no previous medical history. She was married to her first cousin, with no medical history. She had an uneventful first pregnancy in 2015 and was admitted for uterine contractions at 38 weeks of gestation (WG) with abnormal cardiotocography. An emergency cesarean section was performed, which resulted in the birth a boy weighing 3300 grams, Apgar 3/3/3.

The child was transferred to neonatal intensive care unit and placed in controlled hypothermia. The biological assessment showed severe anemia at 4.3 g/dL requiring erythrocyte transfusion. Initially, no etiology was found following routine investigation. A blood count was performed at two months of age due to of skin pallor and found a severe anemia at 3 g/dL, associated with pancytopenia, with a normal myelogram. A genetic workup at 18 months of age revealed a PK deficiency linked to a homozygous p.Tyr433Stop (NM_000298.6(PKLR)c.1299 C>A) mutation in exon 10 of the PK-LR gene. Both parents were then tested for this mutation: they were both heterozygous for the same p.Tyr433Stop mutation in exon 10 of the PK-LR gene. The child received monthly transfusion support until 26 months of age and then received chemotherapy followed by allogenic bone marrow transplantation (paternal origin) at 28 months. The main complication was a grade 3 corticosteroid-sensitive cutaneous graft versus host (GVH) disease. He did not require any further blood transfusions.

For the second pregnancy, an amniocentesis found a fetus free of PK deficiency and she delivered a healthy boy. For her third pregnancy, the couple opted for an amniocentesis at 19 WG, which revealed a PK deficiency in the homozygous state for the familial mutation p.Tyr433Stop.

The pregnancy was monitored at the Armand Trousseau Hospital in Paris, in France. The case was discussed during multidisciplinary meeting at 24 WG to assess whether a hematopoietic stem cell transplantation could be of therapeutic interest in the antenatal period in case of severe fetal anemia to reduce the number of intrauterine and postnatal red blood cells (RBC) transfusions. The indication was not sustained. Ultrasound monitoring was recommended from 24 WG to detect fetal anemia by measuring the peak systolic velocity in the middle cerebral artery (MCA-PSV). [6,7] At 28 $^{+1}$ WG, MCA-PSV was measured at 1.66 MoM and a first

IUT was performed following our local protocol described elsewhere. [8,9] The blood count at the beginning of the procedure showed severe anemia at 6.6 g/dL, accompanied by hematopoietic responsiveness with an increase in reticulocytes and nucleated red cells (regenerative anemia) and increased bilirubin at 80 μmol/L. An intravascular transfusion of 50 mL of RBC was performed at placental cord insertion on a posterior placenta, under ultrasound guidance. Enzymatic assays were performed on fetal RBC collected just before IUT. [10] PK activity was moderately depressed with a strongly depressed PK/Hexokinase ratio, confirming the diagnosis of PK deficiency. At the end of the procedure, the hemoglobin level was 14.5 g/dL and MCA-PSV normalized. Weekly monitoring revealed a further rise in MCA-PSV at 31^{+6} WG (1.72 MoM), requiring a second IUT. Initial blood count revealed severe anemia at 8.9 g/dL, with a consistently high reticulocyte count. An intravascular transfusion of 80 mL enabled to increase the hemoglobin level to 15.3 g/dL (Table 1 and Figure 1).

A cesarean section was scheduled at 37 WG for a history of 2 cesareans, giving birth to a girl weighing 2730 grams, Apgar 10/10/10. Hemoglobin was at 13.6 g/dL on peripheral sampling. The child presented neonatal jaundice with a progressive rise in total bilirubin (Supplemental table 1). Continuous intensive phototherapy was required for 72 hours. The child was discharged home at 5 days of age with folic acid 5 mg three times a week and iron supplementation. She received RBC transfusions at D12 for a hemoglobin of 7.6 g/dL, then at D34 and D63, and every 4 weeks. To date, the child is doing well and is followed regularly by hematologists. It is planned to carry out an HLA typing soon in anticipation of a bone marrow transplant as performed in her brother.

Discussion

PK deficiency is the leading cause of chronic congenital non-spherocytic hemolytic anemia in the world. However, this glycolysis enzyme defect is difficult to diagnose when it is the first case in a family. To our knowledge, only one case of prenatal management of fetal anemia due to PK deficiency has been described in detail in the literature with a diagnosis made prenatally by fetal blood sampling (FBS). [11] This case was reported before the development of PK-LR genetic testing and measurement of MCA-PSV to detect fetal anemia.[12] The FBS was not followed by an IUT and a cesarean section was performed 24 hours after the FBS.[12] Furthermore, among 56 families affected with PK deficiency, the French reference center reported that one fetus was thoroughly monitored during the third trimester of pregnancy and transfused *in utero*, without any information on prenatal management, as this was outside the scope of the study. [4] Recently, the Pyruvate Kinase Deficiency Natural History Study (PKD-NHS), a multicenter, international registry gathering 255 patients with PK deficiency from 2014 to 2017, reported 8 cases of hydrops fetalis and 20 cases treated with IUT, without specifying gestational ages and hemoglobin levels at the time of the procedures. [3] Our case is original, as it is the first to report exhaustively ultrasound and biologic parameters of IUTs in this indication.

Prenatal diagnosis of PK deficiency is usually requested in families with a child suffering from severe neonatal disease. [4] The objective of early invasive prenatal diagnosis is to identify affected fetuses and allow a better management of anemia in the perinatal period. [4] Then weekly ultrasound examinations enable to detect fetal anemia to perform IUT before the occurrence of complications of severe anemia, such as hydrops fetalis and potential brain damage due to decreased cerebral oxygenation. [13] As the risk of complication related to IUT is around 2% per procedure, it must be done optimally both when fetal anemia is severe and

before the appearance of hydrops, with a view, ultimately, to prolonging the pregnancy after 37 weeks. [14] In our case report, the first sibling was born in poor conditions, as fetal anemia and PK diagnosis were not suspected before birth. This infant received emergency transfusion and presented encephalopathy requiring neonatal controlled hypothermia. When another sibling is again affected with PK deficiency, parents are interested in genetic counselling to find out whether the disease will be as severe as that of the previous child. The PKD-NHS provided information on the postnatal severity of the disease among siblings and found that in 74% of the families, siblings were homogeneous in terms of need for splenectomy and transfusion. [3] However, the PKD-NHS study did not provide information on the recurrence of fetal anemia in siblings. Moreover, the authors found that the PK-LR genotype did not correlate with the frequency of *in utero* complications (including hydrops and/or IUT) or in the newborn period (including exchange transfusion and/or phototherapy).[3]

Even though the most common situation is to have an index case of severe neonatal anemia in the sibling, the first affected child in a family may also be diagnosed in the prenatal period during the monitoring of the pregnancy. Our case report emphasizes the importance to perform a complete workup for fetal anemia when no etiology is known at the time of first IUT. The analysis of each case with fetal anemia of unknown diagnosis at the time of indication for IUT should rely on an expert fetal ultrasound examination, parental investigation (family history of hematological disorders), and complete FBS. The workup performed in our centre to investigate severe fetal anemia of unknown cause at the time of the first IUT is outlined in Table 2.[15] Fetal medicine specialists and neonatologists should be aware that some specific tests performed on FBS will be instructive only if they are performed prior to the first IUT in fetuses and before the first transfusion in infants. [5] Indeed, the contribution of PK activity

from normal donor red cells in recently transfused patients is also a relatively common cause of false negative results. This leads to delayed diagnosis in children requiring iterative transfusions.[12] FBS and immediate IUT allow the investigation of the etiology of anemia and its prognosis and reduce prematurity and its associated risks. [15]

In our case, the benefits and risks of *in utero* hematopoietic cell transplantation (IUHCT) were discussed antenatally, but this therapeutic option was not sustained. Indeed, IUHCT would not have changed the perinatal prognosis in an experienced center in IUT practice. Moreover, all the supply chain prior to the implementation of this prenatal therapy would have been long and cumbersome, as it required knowledge of the HLA typing of the fetus through a first FBS before transplantation and seeking compatibility with the parents. Furthermore, the effectiveness of the transplant was not certain. In our case, we chose to perform IUT at 28 weeks because the fetus presented elevated MCA-PSV at ultrasound, which was in favor of moderate to severe fetal anemia. Without this IUT, its anemia would have very likely evolved to hydrops, which is an independent sign of impaired neurodevelopmental prognosis.[16] We performed a second IUT at 31 weeks to prolong the pregnancy until 37 weeks. However, the number of IUTs should be limited as much as possible, because of the risk of procedure complication, leading to emergency cesarean. In fetal hemolysis related to RBC alloimmunization, it has been demonstrated that multiple IUTs cause an exponential decrease in fetal reticulocyte counts and that suppression of the compensatory erythropoiesis leads to prolonged postnatal anemia and an increased requirement of RBC transfusions after birth. [17] In our case, IUTs did not impact erythropoiesis in the postnatal period, since this mutation of the PK gene leads in any case to ineffective erythropoiesis from birth and to the need to continue regular transfusion support from the first days of life.

Conclusion

Fetal anemia related to PK deficiency is rare cause of fetal anemia. When a proband is identified in a family, investigation of the pathology in the fetus is warranted, to set up appropriate ultrasound surveillance and perinatal management. Indeed, severe fetal anemia can occur as early as 28 WG. When a fetus presents with severe anemia of unknown origin, the workup on fetal blood sampling before IUT should comprise the search for red cells enzymopathies, such as PK deficiency. IUTs appear to be a good therapeutic option for PK deficiency, allowing a safer full-term delivery.

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	Gilsanz et al 1993 [12]	Our case	
Intrauterine procedures	**FBS**	**IUT n°1**	**IUT n°2**
Gestational age (WG)	30	28	31
Kleihauer test pre-IUT (%)	NA	100*	39
Pre-IUT Haemoglobin (g/dL)	6.4	6.6	8.9
Mean corpuscular volume (fL)	117	130	99
Red blood cells ($.10^{12}$/L)	NA	1.26	2.68
Reticulocytes (G/L) (Percentage of red cells)	1539 (95%)	386.4 (30.67%)	341.7 (12.75%)
Erythroblasts (G/L) (Percentage of red cells)	0.92 (NA)	0.19 (7.9%)	0.96 (26.6%)
Leukocytes (G/L)	NA	2.4	3.6
Platelets (G/L)	NA	219	262
Blood smear for red cell morphology	macrocytosis with echinocytes and acanthocytes	No morphologic anomalies	No morphologic anomalies
Total Bilirubin (µmol/L)	NA	80	71
Lactate Dehydrogenase (U/L)	NA	185	245
Erythrocyte G6PD (IU/g of hemoglobin)	26.55 (NR: 8.5 $\pm$ 1.6)	27.0 (NR: 11-17)	Not done
Erythrocyte PK (IU/g of hemoglobin)	No measurable activity **	13.1 (NR: 14-19)	Not done
Hexokinase (IU/g of hemoglobin)	NA	4.2 (NR: 0.74-1.14)	Not done
Blood group	A RH:1	O RH:1	Not done
Direct antiglobulin Test	negative	negative	negative
Hemoglobin electrophoresis	normal	normal	Not done
Kleihauer test post-IUT (%)	NA (no IUT)	36	20
Post-IUT Haemoglobin (g/dL)	NA (no IUT)	14.5	15.3

Table 1: Fetal biologic parameters in fetal blood of fetuses affected with pyruvate kinase deficiency

Legend: IUT: intrauterine transfusion; NA: not available; NR: normal range; PK: pyruvate kinase; WG: Weeks of gestation

*The objective of the Kleihauer tests on fetal blood is to assess for the quality of the sampling. The first Kleihauer test at 100% confirms that the fetal blood sampling is pure and not contaminated by maternal red blood cells. The other Kleihauer tests help to monitor the

proportion of fetal blood and donor blood (of adult origin) before and after the subsequent IUTs over time.
**At birth (within 24 hours after the fetal blood sampling), PK activity was <1. In their case report, PK activity was measured as µmol of substrate / hour /g of hemoglobin.

	FETAL BLOOD SAMPLING	BLOOD TUBE	DIAGNOSIS
FIRST LINE INVESTIGATION			
	- Complete blood count and reticulocyte count - Blood smear for red cell morphology	EDTA 0.5mL	*To assess the diagnosis, severity and type of anemia (peripheral or central)*
Central anemia §			
	B19 parvovirus and CMV PCR ±	EDTA 0.5mL	B19 parvovirus or CMV congenital infection
Peripheral anemia §§			
	- Fetal blood group typing - Direct antiglobulin test	EDTA 0.5mL	RBC incompatibility
SECOND LINE INVESTIGATION			
Central anemia §			
	Karyotype *± CGH array *	Sodium heparin 1mL EDTA 2mL	Chromosomal cause, associated or not with myeloproliferative disorder
	Hemoglobin electrophoresis Molecular testing for globin genes analysis	EDTA 0.5mL Sodium heparin 0.5mL	Hemoglobinopathy (major alpha-thalassemia or Hb Bart's disease)
	NGS for rare anemias such as DBA or CDA	EDTA 0.5mL	DBA ; CDA
	Treponema Pallidum PCR ±	EDTA 0.5mL	Congenital syphilis
Peripheral anemia §§			
	Assay of G6PD and PK activities	EDTA 0.5mL	Erythrocyte enzyme disorders: G6PD and PK deficiencies
	EMA test, ektacytometry	EDTA 0.5mL	RBC membrane disorders: poïkilocytosis, pyropoïkilocytosis, spherocytosis, elliptocytosis
BANKING FOR FURTHER ANALYSIS			
DNA banking	DNA banking	EDTA 2mL	

Table 2: Investigation on fetal blood sampling before first intrauterine transfusion

Legend: CDA: Congenital Dyserythropoietic Anemia; CGH: Comparative Genomic Hybridization; CMV: cytomegalovirus; DBA: Diamond-Blackfan Anemia; DNA: desoxyribonucleic acid; EDTA: ethylenediamine tetraacetic acid; EMA test: flow-cytometry for the eosin 5' maleimide acid test; PCR: polymerase chain reaction; RBC: red blood cell

§ Central anemia is due to underproduction of red cells. In the setting of fetal anemia, an aregenerative anemia is defined as anemia associated with a low absolute reticulocyte count, usually below 150 G/L. [15]
§§ Peripheral anemia is anemia accompanied by hematopoietic responsiveness. It implies a response of the fetal liver and spleen to either increased red blood cells destruction (hemolysis) or acute or chronic blood loss. In the setting of fetal anemia, a regenerative anemia is defined as anemia associated with a high absolute reticulocyte count, usually above 150 G/L. [15]
In the setting of normal hemoglobin, the reticulocyte count is expressed as a percentage of the total number of RBCs, with a normal relative reticulocyte count around 1-2%.

± In case of intrauterine transfusion with a posterior placenta, the amniotic fluid is easily accessible without performing a second intrauterine punction for amniocentesis. Therefore, it is preferable to collect amniotic fluid for the following tests: B19 parvovirus, cytomegalovirus, syphilis PCR, and cytogenetic workup. The objective is to spare fetal blood in a fetus which is supposed to be severely anemic. However, for the other tests, it is crucial to perform them on blood of fetal origin.

*Cytogenetic investigation (karyotype and CGH array) can be performed if the parents ask for it after genetic counselling.

	H1*	**H2***	**D2****	**D4****	**D5****
Total bilirubin (µmol/l)	81	114	106	274	176
Conjugated bilirubin (µmol/l)	9	9	15	13	17
Haemoglobin (g/dl)	13.6			11.9	
Mean corpuscular volume (fL)	96			98	
Reticulocytes (G/L)	467			417	
Platelets (G/L)	325			351	
Leucocytes (/mm3)	14 210			8720	

Supplemental table 1: Biological parameters of the newborn from birth to fifth day of life

*H: hours of life; **D: days of life.

Figure legends:

Figure 1: Evolution of the peak systolic velocity in the middle cerebral artery as a function of gestational age

Legend: Hb: hemoglobin; IUT: intrauterine transfusion; MCA-PSV: peak systolic velocity of the middle cerebral artery; WG: Weeks of gestation

MCA-PSV are expressed in cm/sec. Hemoglobin levels are expressed in g/dL.