Eur J Pediatr (2000) 159: 481–482

ORIGINAL PAPER

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Hydrops fetalis associated with erythrocyte pyruvate kinase deficiency

Received: 15 November 1998 / Accepted in revised form: 17 April 1999

Abstract The authors report a case of hydrops fetalis due to severe pyruvate kinase deficiency, the most unusual clinical manifestation of this disease.

Conclusion Pyruvate kinase deficiency, as other erythrocyte enzymopathies, must be considered in the differential diagnosis of non-immune hydrops fetalis. This has important implications for clinical investigations, therapy and genetic counselling.

Key words Pyruvate kinase · Haemolytic anaemia · Hydrops fetalis · Mutations

Abbreviations *G6PD* glucose-6-phosphate dehydrogenase · *GPI* glucose phosphate isomerase · *PK* pyruvate kinase · *PKD* pyruvate kinase deficiency

Introduction

Erythrocyte pyruvate kinase deficiency (PKD) is the most common cause of hereditary nonspherocytic haemolytic anaemia [1]. Although the severity of the anaemia varies greatly, newborns with the disease often require exchange transfusions and, rarely, severe deficiency can cause hydrops fetalis and early neonatal death [4, 5]. We report a case of hydrops fetalis due to severe PKD.

Case report

A newborn girl (aged 5 h) was admitted to our Intensive Care Unit because of hydrops fetalis. She resulted from the second uncomplicated pregnancy of young, healthy and non-consanguineous parents. She was born at 40 weeks by spontaneous delivery with a birth weight of 3500 g. The Apgar score was 6 and 7 after 1 and 5 min; she was pale, hypotonic with generalised oedema, hepatosplenomegaly and respiratory distress.

Laboratory studies revealed severe anaemia (Hb 3.9 g/dl) with reticulocytosis (390×10^9/l) and erythroblastosis (339/100 leucocytes), thrombocytopenia (100,000/mm^3 platelets), hyperbilirubinaemia and metabolic acidosis. The blood group was O Rh (D) positive; the direct Coombs test and the Kleihauer-Betke test were negative. The blood smear showed erythroblastosis without specific morphological alterations. The erythrocyte glycolytic enzyme activities revealed a pyruvate kinase (PK) activity of 9.45 IU/g Hb and twice normal values for glucose-6-phosphate dehydrogenase (G6PD) and glucose phosphate isomerase (GPI) (Table 1). An exchange transfusion was performed after admission and she was ventilated for 48 h. Since 4 months of age she has had severe haemolytic anaemia dependent on regular transfusions.

Table 1 Glycolytic enzyme activities in erythrocytes

	Index case	Father	Mother	Normal range (n = 20)
G6PD (IU/g Hb)	15.6	11.0	7.0	7.5 ± 2.3
PK (IU/g Hb)	8.9	3.7	5.0	9.35 ± 3.05
GPI (IU/g Hb)	80.6	42.5	41.3	44.0 ± 5.0

The parents had no anaemia or reticulocytosis and presented normal erythrocyte morphology. Their PK activities were in the heterozygous range (father 3.7 IU/g Hb; mother 5.0 IU/g Hb). The sister had normal activity. Molecular analysis indicated compound heterozygosity for a previously described mutation 993 A (331 Asp → Gln) and for a new one 1022 A (341 Gly → Asp) [3].

Discussion

Diagnosis of PKD is based on the demonstration of reduced activity or qualitative anomalies of the specific

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erythrocyte enzyme, since most patients have less than 25% of normal activity [6].

Detection is particularly difficult in newborn babies with severe haemolytic anaemia and high reticulocytosis, as reticulocytes have high enzyme activity. Thus, the average enzyme activity of young cells in the circulation must be related to the activities of other age-related enzymes such as hexokinase, GPI and G6PD. In our patient, erythrocyte PK activity was almost normal; however, when taking into account the extremely high values of the other enzymes (G6PD and GPI), it was only 40.6% of the expected value. Also the parents were asymptomatic carriers, strongly suggesting PKD as the cause of anaemia in the baby [4–6].

Recently, various PK gene mutations have been reported [1–3] providing useful information on both the diagnosis and the prognosis of PKD anaemia. In our case, the fact that she was heterozygous for a new mutation did not allow us to establish prognostic criteria.

Erythrocyte enzymopathies, especially PKD, must be considered in the differential diagnosis of non-immune hydrops fetalis, which may have important implications for clinical investigations and therapeutics, including in utero transfusions, as well as for genetic counselling [1].

Acknowledgment The authors are very grateful to Professor Ernest Beutler, Department of Molecular and Experimental Medicine, The Scripps Research Intitute, who provided the molecular study of this patient and kindly reviewed the paper.

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