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Hereditary Pyropoikilocytosis and G6PD Deficiency in a Female Infant Revealed by Recurrent Haemolytic Anaemia

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Abstract

The occurrence of haemolytic anaemia in an infant in the absence of an infectious cause raises the possibility of a red cell intrinsic disorder. Once the most common of these, sickle cell disease, has been excluded, the aetiological investigation should focus on enzymatic deficiencies and red blood cell membrane disorders. We report the case of a female infant in whom simultaneous diagnoses of glucose-6-phosphate dehydrogenase (G6PD) deficiency and hereditary pyropoikilocytosis were established during the investigation of haemolytic anaemia. **Case Report:** MO is a female infant born on 22 July 2023 who was referred to the haematology clinic following recurrent episodes of haemolytic anaemia. Her mother reported that, two weeks after birth, the infant developed cutaneous and conjunctival jaundice. Investigations revealed severe anaemia, with a haemoglobin level of 5 g/dL, for which she was hospitalised and transfused with two paediatric units of packed red blood cells (PRBCs). At five months of age, follow-up revealed splenomegaly classified as stage II and a haemoglobin level of 5 g/dL. A further episode of haemolysis occurred at seven months of age, with the haemoglobin level remaining at 5 g/dL. Sickle cell disease was excluded in both the infant and her parents. Following referral to haematology, enzymatic testing showed G6PD deficiency, with a level of 6.7 U/gHb (normal range: 10 - 14.2 U/gHb). Pyruvate kinase activity was high, while the peripheral blood smear showed findings suggestive of pyropoikilocytosis. Analysis of the parents' blood smears identified elliptocytosis in the mother. **Conclusion:** In a setting where the main causes of haemolytic anaemia are malaria and sickle cell disease, the aetiological investigation in infants

should not be limited to these conditions. The possibility of an intrinsic red cell disorder should prompt investigation for an enzymopathy or a red blood cell membrane disorder. Peripheral blood smear examination remains essential and should precede molecular biological testing.

Keywords

Haemolytic Anaemia, G6PD Deficiency, Hereditary Pyropoikilocytosis, Female Infant

1. Introduction

The aetiological investigation of haemolytic anaemia in general requires a rigorous diagnostic approach including both common causes and those that are much rarer [1]. In newborns and infants, apart from infections, corpuscular causes should be considered, particularly in cases of recurrent haemolytic anaemia. Depending on the geographical location, these causes vary.

Thus, in Africa, where the prevalence of the sickle cell gene may reach 25%, this disease is often considered first. Other corpuscular haemolytic anaemias of membranous or enzymatic origin are considered less frequently, despite the severity of their clinical and biological manifestations. This is the case with hereditary pyropoikilocytosis, a haemolytic disease of the red blood cell membrane characterised by the presence of elliptical-shaped red blood cells on the blood smear. It is thought to result from the transmission of a variant of the **SPTA1** gene, which encodes α-spectrin, or **SPTB**, which encodes β-spectrin. Clinical manifestations range from asymptomatic carriage to transfusion-dependent haemolytic anaemia [2].

G6PD deficiency is by far the most common enzymopathy. In Africa, its prevalence among newborns presenting with jaundice is estimated at 24.6%, with frequencies ranging from more than 40% in Nigeria to less than 4% in South Africa [3]. It is common in males, whereas females transmit it through their X chromosome [4]. Women are rarely symptomatic, apart from a few cases reported in the literature [5]. Clinical manifestations include signs of anaemia, often with sudden onset, and haemolysis, predominantly characterised by jaundice. During the neonatal period, jaundice is the main mode of presentation of G6PD deficiency.

In Gabon, haemolytic anaemias have two main aetiologies: one infectious and parasitic, namely malaria, and the other related to a haemoglobinopathy, namely sickle cell disease. Although Gabon is an area where G6PD deficiency is endemic, this aetiology is rarely considered, even less so in girls. We report the case of a female infant seen for haemolytic anaemia whose investigation led to the concurrent diagnosis of pyropoikilocytosis and G6PD deficiency.

2. Observation

MO is a female infant born on 22/07/2023 who was referred to the haematology clinic by her paediatrician in March 2024 for haemolytic anaemia. The mother

reported that, two weeks after birth, the child developed cutaneous and conjunctival jaundice. She was taken to a neonatal consultation, where investigations revealed anaemia with a haemoglobin level of 5 g/dL, reticulocytes were not available before transfusion, for which she was hospitalised and transfused with two paediatric packed red blood cell units (PRBCs). She was discharged when her haemoglobin level had reached 9.7 g/dL.

A recurrence of the same clinical presentation was observed at the age of 5 months, this time with the palpation of marked splenomegaly classified as stage II according to the HACKETT classification. At the age of seven months, she was hospitalised again following anaemia with a haemoglobin level of 5.1 g/dL, associated with conjunctival jaundice and dark urine. After being transfused with one unit of PRBCs, the infant was subsequently referred to the haematology clinic. Malaria testing was performed at each hospital admission, while a direct antiglobulin test was performed prior to each blood transfusion. All tests were negative.

The investigations revealed, on clinical examination, splenomegaly and, biologically: white blood cells 9282/mm^3, haemoglobin 6.4 g/dL, platelets 470,000/mm^3, serum iron 25.8, ferritin 684 ng/mL, haptoglobin < 0.08 g/L, total bilirubin 44 IU/L and unconjugated bilirubin 34 IU/L. Haemoglobin electrophoresis of the infant and her parents is presented in Table 1.

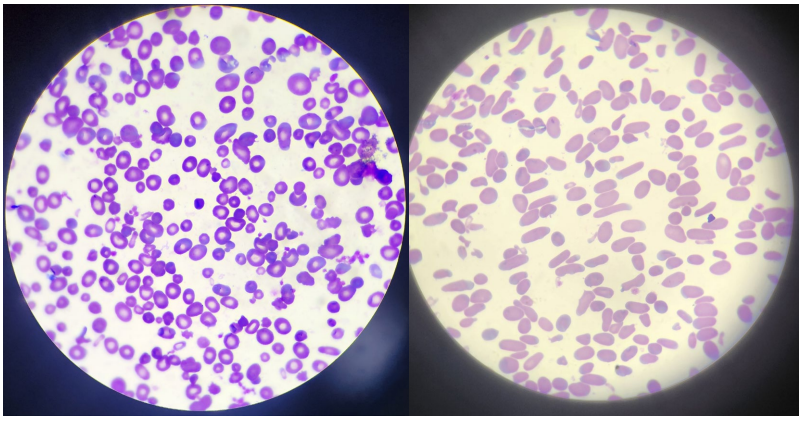
Table 1. Haemoglobin electrophoresis of the infant and her parents.

Haemoglobin (%)	Father	Mother	Infant
Haemoglobin A	97.2	95.2	92.3
Haemoglobin A2	2.8	4.8	2.3
Haemoglobin F	—	—	5.4

More than two months after the transfusion and a hospitalization for hemolysis and anemia, the exclusion of sickle cell disease led to G6PD and pyruvate kinase assays. The **G6PD** was at **6.7 U/gHb (normal 10 - 14.2 U/gHb)**; pyruvate kinase at 68.1 U/gHb (N: 7.6 - 28.6 U/gHb); G6PD/pyruvate kinase ratio 0.1 (a ratio < 0.49 is in favour of G6PD deficiency). At this time reticulocytes count was normal. There was no deficiency in the mother (**G6PD 12.4 U/gHb**).

The blood smear showed marked anisopoikilocytosis with ovalocytes, erythrocyte fragments and microspherocytes. The appearance of the blood smear was suggestive of a constitutional red blood cell abnormality consistent with pyropoikilocytosis (Figure 1(A)). The mother's blood smear showed numerous elliptocytes (Figure 1(B)) and was normal for the father.

The definitive presumptive clinical diagnosis was **hereditary pyropoikilocytosis associated with G6PD deficiency**. This diagnosis was considered given the recurrent nature of the hemolysis, the severity of the anemia, the splenomegaly, and the anisopoikilocytosis observed on the blood smear of patient and elliptocytosis in the mother.



(A) (B)

Figure 1. Blood smear of the patient (A) and her mother (B).

Following the diagnosis, a regular follow-up programme in the haematology and paediatric outpatient clinics was established. The patient was started on folate supplementation. The diagnosis was explained to the parents, and they were provided with a list of foods and medications requiring caution. The proposed splenectomy and its potential benefits were also discussed with them.

The parents provided consent for the use of their own data and that of their child prior to manuscript preparation.

3. Discussion

In the present case, jaundice was observed fifteen days after birth and led to the first transfusion. The early onset of this neonatal haemolytic anaemia, even in a country with a high prevalence of sickle cell disease (21% in Gabon), [6] should prompt consideration of another cause, as the diagnosis of this disease at this age is not definitive. Foetal haemoglobin provides protection to the newborn until the age of 6 months. Furthermore, the hand-foot syndrome, the main clinical sign, was not identified during questioning of the parents or examination of the child.

Repeated transfusions constituted a difficulty in excluding sickle cell disease, since electrophoretic diagnosis cannot be considered within the three months following a transfusion. The infant received one transfusion on average every three months, making it impossible to perform the test. Testing of the parents ultimately made it possible to definitively exclude this diagnosis.

G6PD deficiency is an inherited enzymopathy linked to the X chromosome, in which only males are affected. Symptomatic females may occur through skewed X-chromosome inactivation or biallelic pathogenic variants. Rare cases of symptomatic females have been reported [7]. Gabon is an area of high endemicity. Screening for the condition is strongly recommended in cases of haemolytic anaemia. In the case described here, the child's sex should have constituted an argument against this condition, since only male individuals are known to develop the disease. It was therefore unlikely to be responsible for the clinical presentation. However, genuine cases reported in the literature do not allow this diagnosis to

be formally excluded. The authors describe the young age at onset, the appearance of jaundice during the first months of life and elevated bilirubin levels [7]. Nevertheless, the involvement of G6PD deficiency in the occurrence of the clinical presentation should be interpreted with caution because of its association with another corpuscular haemolytic anaemia.

Indeed, hereditary pyropoikilocytosis belongs to a heterogeneous group of red blood cell abnormalities responsible for haemolytic anaemia. The individual inherits mutated genes from their parents that are responsible for a deficiency of a membrane protein. Clinical manifestations are variable, ranging from haemolytic anaemia presenting very early, often a few days after birth in the form of neonatal jaundice, to an absence of manifestations.

In its asymptomatic form, pyropoikilocytosis is often detected through analysis of the peripheral blood smear. In symptomatic individuals, there is usually a combination of findings suggesting the disease: onset during the neonatal period, clinical and biological signs of haemolysis, and the presence of elliptocytes on the blood smear. This is what was reported in the present case. This examination made it possible to establish the hereditary nature of the elliptocytosis, in addition to the timing of onset of the first signs, in the context of this case in which molecular analysis could not be performed.

Indeed, analysis of the mother's blood smear revealed numerous elliptocytes, even though she was asymptomatic and reported no history of haemolysis during childhood. Examination of the parents' blood smears is an important step before undertaking any molecular analysis [8]-[10]. For Flavio Augusto Naoum, as in the present case, pyropoikilocytosis was associated with another inherited red blood cell disorder (beta-thalassaemia), the consequence of which was increased haemolysis due to an abnormality of haemoglobin and a deficiency of a membrane protein [11]. Molecular diagnosis generally makes it possible to identify a mutation in the gene encoding spectrin [12] [13]. Treatment in forms causing acute haemolysis with severe anaemia is based on folic acid administration and splenectomy [14] [15].

4. Conclusion

The aetiological investigation of haemolytic anaemia, even in areas where malaria is endemic or where sickle cell disease is highly prevalent, should include the investigation of other corpuscular causes. The blood smear, a routine and key examination for many red blood cell disorders, should form the basis of the diagnosis before more extensive investigations are considered. Extending blood smear examination to the parents may provide useful diagnostic evidence. The high frequency of their presentation during the neonatal period raises the question of the widespread use of rapid diagnostic tests for their detection.

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Author Contributions

Conceptualization, M.I. R.I.N and Y.N.; methodology, M.I.; validation, M.I., C.S., and L.E.L; formal analysis, M.I.; investigation, M.I.; data curation, M.I.; writing—original draft preparation, M.I.; writing—review and editing, M.I.; visualization, M.I.; supervision, M.I.; All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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