

A rare cause of
icterus prolongatus



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Title figure:

Richard Cremer (left) and Sister Jean Ward (right),
Rochford General Hospital, Rochford, Essex, UK,
are credited with the discovery of phototherapy to
treat neonatal jaundice

(sources: photograph left – www.bmj.com and
photograph right – www.schematicscholar.org)

INTRODUCTION

Jaundice due to unconjugated hyperbilirubinemia is very common in neonates. Although not the most common cause, hemolysis is regularly seen. Occasionally, congenital red blood cell disorders are responsible. In this report, we present the case of a neonate with icterus prolongatus, who was eventually diagnosed with dehydrated hereditary stomatocytosis, a rare inherited hemolytic disorder of the erythrocyte membrane.

CASE REPORT

This female infant was born at 37 0/7 weeks of gestation with a birth weight of 2995 g. She was the first child of a healthy 30-year-old woman from Germany and her likewise healthy partner from Kosovo. There were no known genetic disorders in either family, especially no known cases of jaundice or blood disease.

The girl was born via vaginal birth with an Apgar Score of 5, 7 and 8 at 1, 5 and 10 minutes, respectively. She was hospitalized in our neonatology unit from the 1st to 4th day of life (DOL) due to respiratory distress, which required CPAP support and oxygen supplementation. She was started on a course of antibiotics following prolonged rupture of membranes and a positive maternal *Streptococcus agalactiae* swab, with cessation of treatment when blood cultures remained negative after 48 hours. Notably, a complete blood count done on DOL 2 was normal.

At discharge, the girl was fed breast milk as well as formula milk (Aptamil Pre®). She was readmitted on DOL 6 due to hyperbilirubinemia for a first course of phototherapy, to which she responded well. She was discharged 2 days later. When her jaundice persisted, she was readmitted for phototherapy on DOL 11.

Given its prolonged course, further investigations were performed to evaluate the cause of hyperbilirubinemia. Conjugated bilirubin concentrations were repeatedly within normal limits. Hypothyroi-

dism was excluded. Sepsis/infection were unlikely given the absence of symptoms. Initially, a complete blood count showed a hemoglobin value at the lower limit of normal with a high reticulocyte count (Hb 131g/l, reticulocytes 85 G/l). When the blood count was repeated on DOL 14, it clearly showed normocytic anemia with persistent reticulocytosis (Hb 101g/l, reticulocytes 79.6 G/l, LDH 418 IU/l, haptoglobin <0.10 g/l), indicating hemolysis as the cause of the prolonged unconjugated hyperbilirubinemia. Red blood cell (RBC) indices, white blood cell and platelet counts were consistently within the normal range, and there was never any suspicion of impaired bone marrow function. There was no blood type incompatibility with negative direct and indirect Coombs' tests on DOL 8 and 18. Glucose-6-phosphate dehydrogenase and pyruvate kinase activities were normal.

There were no hematomas or any other evidence of birth trauma. On sonography, there were no intracranial or intraabdominal hemorrhages, no large intraabdominal hemangiomas, and no signs of splenomegaly. Cytomegalovirus PCR of the urine was negative.

Hemoglobin electrophoresis did not show any variant or abnormal hemoglobin. Due to a high suspicion of an inherited RBC membrane disorder, an osmotic gradient ektacytometry was performed and confirmed the diagnosis of dehydrated hereditary stomatocytosis (DHS) (Fig. 1).

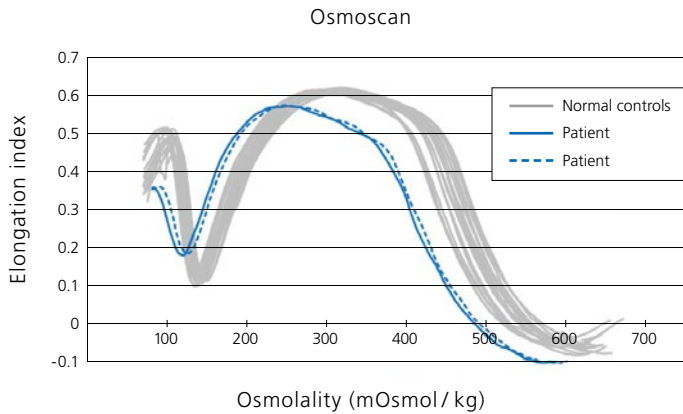


Fig. 1

Osmotic gradient ektacytometry of our patient: note the characteristic left shift of the curve indicating DHS (blue lines). The test measures RBC deformability under a defined shear stress as a function of suspending medium osmolality.

Apart from her jaundice, the infant's anemia was asymptomatic; she received her final course of phototherapy on DOL 14 and was then discharged. At a planned follow-up on DOL 18, there was evidence of ongoing hemolysis (Hb 62 g/l, reticulocytes 122 G/l, LDH 346 IU/l), and she received her first RBC transfusion. A second RBC transfusion was necessary on DOL 37. At 8 weeks of life, the girl was doing well with normal weight gain. Her bilirubin values had shown a gradual and steady decline to normal values, and her hemoglobin values were also stable at around 80–90 g/l.

DISCUSSION

Hereditary stomatocytosis (HSt) is the broader term for a group of congenital RBC disorders associated with chronic hemolysis, characterized by the presence of stomatocytes (erythrocytes with a central 'mouth-shaped' slit rather than circle of pallor) on peripheral blood smear (Fig. 2) (1). The underlying mechanism leading to the formation of stomatocytes is an altered erythrocyte membrane cation permeability caused by dysfunctional membrane proteins, in which an altered cation flux across the membrane leads to changes in RBC volume and subsequently to the characteristic morphological changes (2).

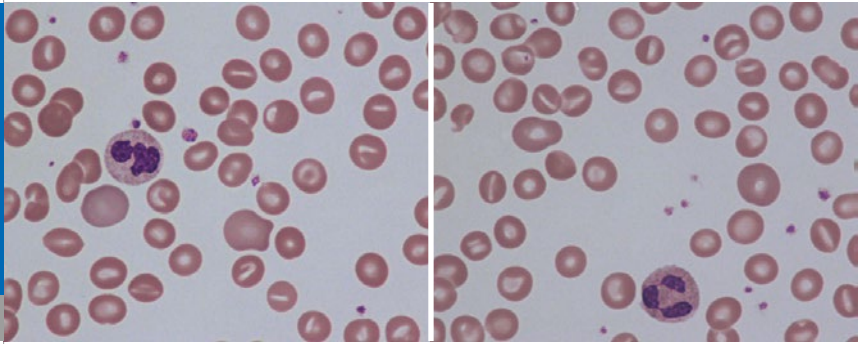


Fig. 2

Peripheral blood smear from a patient (not our patient) with DHS: note the presence of stomatocytes with a central slit rather than circle of pallor (source: Layton DM, Bain BJ. Dehydrated hereditary stomatocytosis. Am J Helmitol 2016;91(2):266).

DHS is the most common form of HSt, although the exact population prevalence is unknown: according to varying literature sources it is estimated between 1:8'000 – 1:50'000, and could possibly be underdiagnosed (2, 3). It was first described in 1971, interestingly in three siblings of Swiss-German ancestry (4). The cause of DHS is genetic, and its inheritance is mainly autosomal-dominant (2). So far, two genes have been identified. The more frequently affected gene, *PIEZO1*, encodes a transmembrane nonselective cation channel of the same name, activated by mechanical stress on the RBC membrane (2, 3). Several mutations of the *PIEZO1* gene leading to the phenotype of DHS have been described (2, 3). Each mutation results in delayed inactivation of the *PIEZO1* channel, leading to increased calcium influx, which in turn results in increased potassium efflux out of the erythrocyte via activation of a separate RBC membrane protein, the potassium selective cation channel called the Gardos channel (3). The subsequent efflux of water via osmotic gradient leads to cell dehydration, fragility and reduced deformability, making the erythrocyte susceptible for lysis and elimination in the spleen (3). The second causative gene is *KCNN4*, which encodes the Gardos channel itself, and here too more than one mutation has been linked to the phenotype of DHS (2, 3).

The clinical presentations of DHS ranges from mild to severe; the great phenotype variability seems to be

partly explained by the genetic heterogeneity of the disorder (2). Classic signs of hemolysis are common, such as jaundice, pallor and eventually splenomegaly, and cholelithiasis (1, 4, 5).

Diagnosis is usually made later in life, but – as with our patient – the disorder can manifest itself in the perinatal period. In the literature, perinatal edema including ascites and pleural effusion but also nonimmune hydrops fetalis have been reported with DHS, and these patients all seem to be affected by a *PIEZO1* mutation (3). The edema is predominantly transient in nature, resolving spontaneously after birth, and its degree is usually mild, although there have been reports of severe disease with hydrops fetalis necessitating prenatal intervention or neonatal intensive care (2, 3).

Laboratory findings include signs of hemolysis with normal or low hemoglobin concentration, reticulocytosis, elevated lactate dehydrogenase (LDH), and elevated unconjugated bilirubin. In our patient, the first notable presentation of the disorder was persistent hyperbilirubinemia into the 3rd week of life. Stomatocytes are visible on peripheral blood smear, but usually only in small numbers (less than 20 % of all RBCs) (2); sometimes, target cells are present (1).

Distinctively elevated MCHC values are common. Specific diagnostic blood tests include *decreased*

osmotic erythrocyte fragility (distinguishing DHS from the much more common hereditary spherocytosis with *increased* osmotic erythrocyte fragility) and characteristic findings in osmotic gradient ektacytometry (1, 3). Although the result of the osmotic gradient ektacytometry in our patient was very suggestive of DHS (Fig. 1), a definitive diagnosis in the neonatal period is difficult as no age adapted norm values exist. Genetic analysis of the *PIEZO1* and *KCNN4* genes is becoming increasingly important in order to confirm the diagnosis (2).

Currently, there are no specific treatments. Since the underlying anemia is usually mild, the majority of patients show little or no symptoms, and the need for regular RBC transfusions is exceptional (1, 3). Interestingly, despite rare transfusion requirements, many patients with DHS eventually develop body iron overload due to a yet unclear underlying mechanism, which – if not treated – can be accompanied by complications such as heart failure, liver fibrosis and pancreatic insufficiency (3). While there is little data on the prevalence of these complications in the pediatric population, adolescents and young adults can be affected (3). Therefore, the need for iron chelation therapy should be regularly assessed when managing a DHS patient. In contrast to other hemolytic disorders, such as hereditary spherocytosis, splenectomy is strictly contraindicated. Current data suggests that most patients with DHS do not benefit from

splenectomy given that their anemia does not significantly improve, while simultaneously their risk of thromboembolic complications drastically increases, almost guaranteeing a thromboembolic event (1–3).

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