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Case report

Early infantile form of galactosialidosis presenting as nonimmune hydrops fetalis: a case report

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Abstract

Case report: A 20-year-old woman was referred to our tertiary center due to hydrops fetalis (HF) diagnosed at 24 weeks of gestation. She had severe acne and underwent treatment with isotretinoin up to a month before pregnancy. The parents were consanguineous. The third trimester ultrasound revealed median volume ascites and generalized subcutaneous edema. Maternal parvovirus B19 serologies showed positive IgG and IgM antibodies. Elective caesarean section was performed at 30 weeks, demanding immediate postnatal resuscitation, including mechanical ventilation and evacuation paracentesis. The newborn had coarse facies, subcutaneous edema, marked abdominal distention, abdominal telangiectasias, mild hypertrophy of the labia minora, short long bones and fourth right toe clinodactyly. The HF next generation sequencing (NGS) gene panel identified a homozygous variant in exon 3 of the *CTSA* gene [NM_000308.4:c.254G>T p.(G85V)]. Biochemical lysosomal study of cultivated amniocytes confirmed the diagnosis of galactosialidosis (GS). Follow-up and palliative care by a multidisciplinary team ensued. Parental genetic testing confirmed carrier status for the aforementioned variant and further genetic counseling was provided.

Discussion: Elucidation of the etiology of non-immune HF is essential for determining treatment and prognosis. Despite being extremely rare, GS is one of the most common lysosomal storage diseases. An early diagnosis allows for better care as well as genetic counseling for future pregnancies. An experienced multidisciplinary team is essential for optimal management.

Keywords

Hydrops fetalis, lysosomal storage diseases, galactosialidosis, genetic counseling, neonatal care, palliative care.

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Case report

A 20-year-old woman was referred to our tertiary center due to hydrops fetalis (HF) diagnosed at 24 weeks of gestation. Her blood type was B Rh negative. Treatment with isotretinoin occurred up to a month before pregnancy due to severe acne. Parents were third degree cousins, with no other relevant family history. The third trimester ultrasound showed median volume ascites and generalized subcutaneous edema, especially of the lower limbs and neck. No additional abnormalities were evident on subsequent evaluations. Prenatal diagnostic workup included fetal Doppler ultrasound, echocardiogram, maternal complete blood count, indirect Coombs test, analyses of abnormal hemoglobin variants by high-performance liquid chromatography (HPLC) and the Kleihauer-Betke test, which were all normal. The toxoplasma, rubella, cytomegalovirus, and herpes simplex virus (TORCH) test and panel for gastrointestinal infections were negative for acute infection, but maternal parvovirus B19 serologies showed positive IgG and IgM antibodies. Amniocentesis was performed at 24 weeks: fetal karyotype and array comparative genomic hybridization were normal and an HF next generation sequencing (NGS) gene panel was ordered.

Two courses of antenatal steroids were administered and an elective caesarean section (C-section) was performed at 30 weeks. Birth anthropometry was appropriate for gestational age (weight: 1,700 grams, 90th percentile). the Apgar score was 6, 7, and 8 at the first, fifth and tenth minutes, respectively. Endotracheal intubation was performed by the first 2 minutes of life due to persistent hypotonia, ineffective respiratory movements and bradycardia. A gradual recovery was evident once invasive ventilation was started. The newborn had coarse facies, subcutaneous edema of the nape of the neck, marked abdominal distention, abdominal telangiectasias, mild hypertrophy of the labia minora, short long bones and fourth right toe clinodactyly (**Fig. 1A** and **Fig. 1B**).

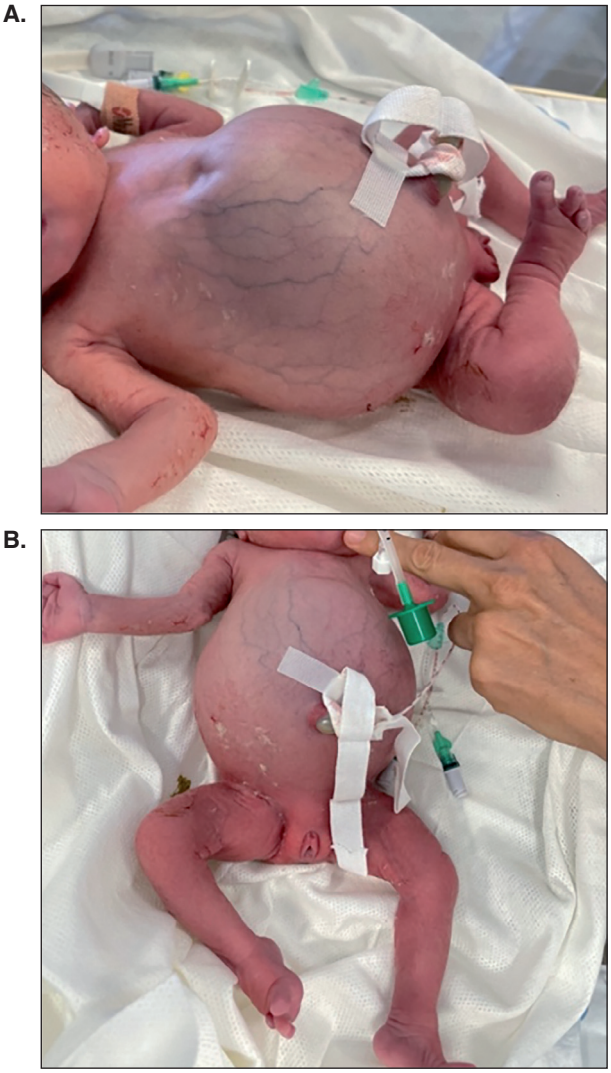

Figure 1. The newborn had coarse facies, subcutaneous edema of the nape of the neck, marked abdominal distention, abdominal telangiectasias, mild hypertrophy of the labia minora, short long bones and fourth right toe clinodactyly.

The result of the HF NGS gene panel was known shortly after birth and disclosed a homozygous variant of uncertain clinical significance in exon 3 of the *CTSA* gene [NM_000308.4:c.254G>T p.(G85V)], associated with galactosialidosis (GS; OMIM #256540). Biochemical lysosomal study of cultivated amniocytes showed reduced enzymatic activity of β-galactosidase 1 (GLB1) and α-neuraminidase 1 (NEU1) and increased sialic acid, therefore confirming the diagnosis. Genetic testing of the parents established their carrier status and confirmed the presence of homozygosity for the aforementioned variant in the newborn.

Hospitalization and management by a multidisciplinary team (neonatologists, pediatricians, geneticists, pediatric cardiologists, ophthalmologists, psychologists, pediatric psychiatrists and rehabilitation therapists) occurred during the first 3 months of life. The patient needed invasive mechanical ventilation for the first 10 days and was adapted to domiciliary ventilation at 2 months. Due to the persistent generalized edema, moderate to large volume ascites and hypoalbuminemia, she needed daily paracentesis for the first 10 days, multiple albumin perfusions and occasional diuretic administration. Abdominal imaging revealed splenomegaly and renal and biliary microlithiasis. Echocardiograms showed signs of slight pulmonary hypertension, a patent foramen ovale and a small anterior pericardial effusion. She needed multiple erythrocyte transfusions due to pancytopenia probably related to underlying leucoerythroblastosis. For the first month, she was kept on parenteral nutrition, and afterwards nasogastric nutrition, due to feeding difficulties, chronic diarrhea and failure to thrive. Serial cranial ultrasounds showed a short corpus callosum, with diffuse hyperechogenicity of the subcortical white matter. Ophthalmological evaluations were normal.

The patient is currently 5 months old and has significant neurological impairment (marked axial hypotonia, little cephalic control, and poor suction reflex and directed look), abdominal and perineal distension, telangiectasis and splenomegaly (**Fig. 2**). She continues to need exclusive nasogastric tube feeding and non-invasive ventilation during sleep, and is kept on diuretic treatment. Follow-up is ensured by a multidisciplinary team, including palliative care. Parents continued follow-up with the Medical Genetics Department and GS enzymatic invasive prenatal diagnosis was made available for future family planning.

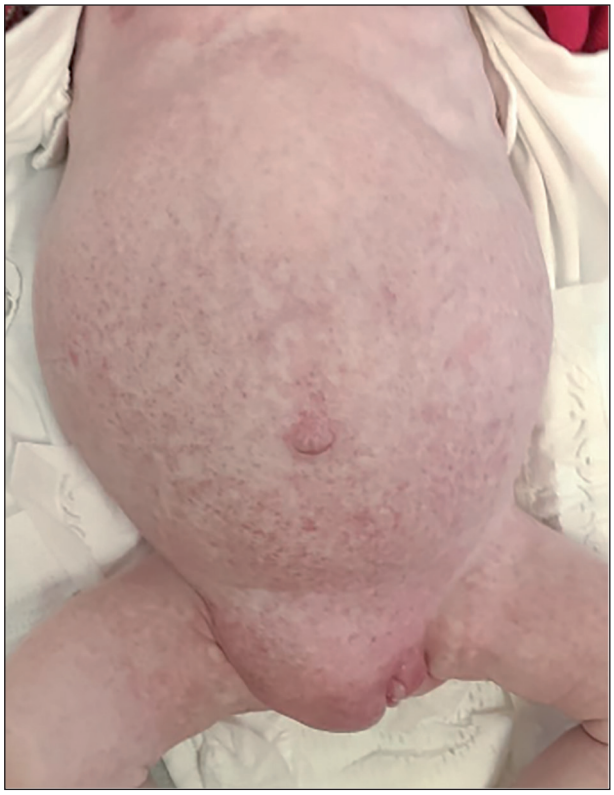

Figure 2. The patient is currently 5 months old and has significant neurological impairment (marked axial hypotonia, little cephalic control, and poor suction reflex and directed look), abdominal and perineal distension, telangiectasis and splenomegaly.

Discussion

HF is characterized by pathologic fluid accumulation in two or more fetal compartments, diagnosed by prenatal ultrasound. Nonimmune hydrops fetalis (NIHF) accounts for almost 90% of cases (prevalence of 1 in 4,000 live births) and refers to causes other than red cell alloimmunization [1, 2].

After diagnosis, antenatal care should be multidisciplinary and different options are considered depending on the gestational age, mother's health and family's beliefs. In this case, the family did not consider termination of pregnancy. An elective C-section was performed and postnatal management was anticipated by an experienced team, considering the possibility of a difficult airway intubation and the need for evacuation paracentesis.

The differential diagnosis of NIHF is extensive and includes prenatal infections, cardiovascular causes, and chromosomal and hematologic abnormalities [1]. An early diagnosis is essential for better counseling, including pregnancy termination consideration, appropriate neonatal management,

possible early treatment and genetic counseling of subsequent pregnancies [2]. Isotretinoin is a potent teratogenic agent associated with congenital anomalies in up to 30% of exposed fetuses, but HF has not been described [3]. On the other hand, parvovirus is the most frequent infectious cause of HF; however, the absence of anemia led clinicians to question whether the infection itself could explain the clinical picture [1]. For these reasons, the history of isotretinoin exposure and serological diagnosis of acute parvovirus B19 infection did not delay subsequent investigation of alternative causes.

The Portuguese national clinical consensus includes assessment of inborn errors of metabolism for cases that remain idiopathic after the initial prenatal workup. Lysosomal storage diseases (LSD) have been reported to account for approximately 1% to 15% of all NIHF cases [2, 4-7]. A retrospective case control study from 2020 reported that the most frequently diagnosed LSD was GS, accounting for about 29% of cases [8]. More recently, a systematic review reported that the overall incidence of LSD was 6.6%, with mucopolysaccharidosis type VII being the most prevalent (23.4%), followed by GS (13.5%), infantile sialic acid storage disease (13%), Gaucher disease (12%), GM1 gangliosidosis (11.5%) and sialidosis (10.4%) [9]. The fact that a diagnosis of LSD was made in 8% of previously considered "idiopathic" NIHF cases underscores the need to include LSD testing as part of the workup for NIHF [9].

GS is an autosomal recessive disorder associated with a combined deficiency of GLB1 and NEU1, secondary to a defect in protective protein/cathepsin A (PPCA) [10]. The true prevalence of GS is unknown, but less than 150 cases are reported in the literature. The early infantile form, reported in around 40 cases to date, usually presents before 3 months. Clinical manifestations are typical of LSD and include HF, visceromegaly, skeletal dysplasia and early death. Telangiectasis can be found almost exclusively in this type and were present in this patient. A total of 36 *CTSA* mutations associated with GS have been identified to date [5, 6].

As GS is rare and potentially underdiagnosed, disease awareness may be rather low. In this case, the HF NGS gene panel identified a homozygous *CTSA* variant of uncertain significance. However, this variant had already been described in compound heterozygosity in patients with GS and had been previously reported in a fetus with HF and biochemical confirmation of GS by our Biochemical Genetics Unit [11]. Moreover, the clinical features were suggestive of LSD (coarse facies, splenomegaly and short long bones). Thus, biochemical lysosomal analysis of cultured amniocytes was promptly initiated and confirmed the diagnosis of GS in the newborn. There is variant heterogeneity at *CTSA* in patients with GS, especially in those with an early infantile phenotype [10]. Confirmation of homozygosity for the aforementioned *CTSA* variant in the newborn was also obtained through parental studies, supporting its pathogenic nature.

The knowledge of the natural course of GS is limited, but patients with the early infantile form usually die within the first year, likely due to heart and kidney failure. Currently, the approach to these patients is focused on managing the symptoms and providing palliative care to patients and families [12]. Gene and enzyme-replacement therapies are currently being examined as potential emergent treatments [13-15].

Declaration of interest

The Authors have no financial interest and no conflict of interest to disclose.

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