Hydrops Fetalis in a Preterm Newborn Heterozygous for the c.4A>G SHOC2 Mutation

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Fetal hydrops is a condition resulting from interstitial fluid accumulation in fetal compartments secondary to increased capillary permeability and characterized by high rates of perinatal mortality and morbidity. Clinical features include skin edema, hydrothorax, pericardial effusion, ascites with or without polyhydramnios, and placental edema. While it may occur as an associated feature in multiple disorders, it has been documented to recur in Noonan syndrome, the most common disorder among RASopathies, but also in cardiofaciocutaneous and Costello syndromes. Here, we report on the occurrence of severe hydrops in a newborn heterozygous for the invariant c.4A>G missense change in SHOC2 which underlies Noonan-like syndrome with loose anagen hair, documenting that it represents a clinically relevant complication in this condition, shared by RASopathies.

Key words: fetal hydrops; Noonan-like syndrome with loose anagen hair; SHOC2; RASopathies

INTRODUCTION

Fetal hydrops is a nonspecific, end-stage status of a wide variety of disorders, of which cardiovascular diseases and chromosome abnormalities are the most frequent causes. Other conditions must not be overlooked, including anemia, intra-thoracic mass, lymph vessel dysplasia, inborn errors of metabolism, twin-to-twin transfusion syndrome, viral infections, urinary tract malformations, extra-thoracic tumors, gastrointestinal disorders, and syndromic conditions. While maternal illnesses must be taken into account, idiopathic origin is common [Chitty, 2003; Bellini et al., 2009].

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Fetal hydrops has a strong impact on the life and health of the newborn owing to high rates of perinatal mortality and morbidity. Fetal hydrops has been recurrently documented in Noonan syndrome (NS) [Lee et al., 2009; Croonen et al., 2013] one of the most common non-chromosomal conditions affecting development and growth [Roberts et al., 2013]. Major features of NS include distinctive facial phenotype, congenital heart disease, post-
natal reduced growth, lymphatic and hematologic anomalies, and variable learning difficulties [Roberts et al., 2013]. Mutations in seven genes encoding proteins involved in the RAS-MAPK signal transduction pathway (PTPN11, SOS1, KRAS, NRAS, RAF1, BRAF, and RIT1) underlie this Mendelian trait [Tartaglia et al., 2001, 2002, 2007, 2010, 2011; Zenker et al., 2004; Carta et al., 2006; Schubbert et al., 2006; Pandit et al., 2007; Razzauque et al., 2007; Roberts et al., 2007; van der Burgt, 2007; Sarkozy et al., 2009a,b; Allanson et al., 2010; Cirstea et al., 2010; Martinelli et al., 2010; Niemeyer et al., 2010; Aoki et al., 2013]. NS is the most common of a family of clinically and pathogenetically related developmental disorders collectively known as RASopathies [Tartaglia and Gelb, 2010]. Within this group of disorders, fetal hydrops has been documented also in cardiofaciocutaneous and Costello syndromes [Grebe and Clericuzio, 2000; Lorenz et al., 2012].

Mazzanti et al. [2003] reported a condition with features partially overlapping NS, which they named Noonan-like syndrome with loose anagen hair (NS/LAH). This phenotype represents a distinctive nosologic entity caused by the invariant c.4A>G missense change (p.Ser2Gly) in SHOC2 [Cordeddu et al., 2009], which encodes a regulatory protein positively modulating RAF1 function [Rodriguez-Viciana et al., 2006]. In the original report, 25 individuals heterozygous for the c.4A>G nucleotide substitution were described, documenting a homogeneous and distinctive phenotype within the RASopathy spectrum [Cordeddu et al., 2009]. While the available clinical records consistently indicate that newborns or young infants with NS/LAH show features more severe than generally observed in NS, complications resulting from lymph vessel anomalies have not been reported. Here we describe the first case of NS/LAH presenting with fetal hydrops.

**CLINICAL CASE**

The propositus is the second-born of nonconsanguineous parents. Family history was negative for malformations or intellectual disability. The first ultrasound scan was performed at 20 weeks’ gestation and showed a nuchal skin fold of 8 mm. The fetal biometry was normal and no other structural anomalies were detected. Fetal echocardiography showed a normal heart for structure and function. Prenatal invasive diagnosis was not performed according to the couple’s choice. An ultrasound examination at 29 weeks of gestation showed polyhydramnios and severe fetal hydrops with diffuse thick cutaneous edema, severe ascites, moderate pleural effusion, and confluent bowel loops (Fig. 1). The pulsatility index (PI) of the umbilical artery was normal. Fetal 1.5 T Magnetic Resonance Imaging confirmed severe hydrops with hydrothorax, ascites, and thickening of the subcutaneous tissue. No brain malformations were found. Amniocentesis demonstrated a normal male karyotype. Infection screening was performed for unexplained hydrops. Serum and amniotic polymerase chain reaction (PCR) test for parvovirus B19, cytomegalovirus, and toxoplasma gondii were negative, as was maternal serology for common infective agents and vagino-rectal swab. Alloimmune causes of hydrops were excluded by Coombs test.

At 29 + 5 weeks’ gestation fetal ultrasound showed persistent polyhydramnios and progressive worsening of fetal hydrops. The PI of the umbilical artery was increased and steroids were administered for lung maturation. Hypertelorism and posteriorly angulated low-set ears were observed.

At 30 weeks 5 days a caesarean was planned due to worsening of all Doppler parameters. At birth, resuscitation was needed. Apgar scores were 4 and 7 at 1 and 5 min, respectively. The baby, mechanically ventilated, was transferred to the Neonatal Intensive Care Unit. Physical exam revealed a large baby for gestational age (weight: 3,000 g, >95th centile; length: 42 cm, 75th centile; head circumference: 34.5 cm, >95th centile; abdominal circumference: 39.5 cm, >95th centile) with generalized edema. Dysmorphic facial features, due in part to massive edema, included hypertelorism, slight downslanting palpebral fissures, and posteriorly angulated low-set ears, with thick helix and up-lifted lobes (Fig. 2). Skin was edematous, stretched, and bright, with thoracic petechiae. He had thin hair. Heart sounds were rhythmic but paraphonic; pulses were bounding. Breath sound was reduced and chest wall movements extremely limited with mechanical ventilation support. Due to

![FIG. 1. A: Ultrasound transverse view showing diffuse thick skin (arrow). B: Severe ascites and conglutinated bowel loops (arrow).](image-url)
swelling and distension, the abdomen was difficult to evaluate. Male genitals with normal penis and undescended testes were observed. Neurologic examination showed severe generalized hypotonia with very poor spontaneous motility. Thoraco-abdominal ultrasound and radiographs within the first hours of life confirmed slight left pleural effusion and severe peritoneal effusion that was extemporaneously drained (with a draw of 315 ml) and a peritoneal drainage was placed due to recurrent ascites (Fig. 3). Peritoneal fluid analysis showed a sterile exudate (serum-ascitic albumin gradient = 0.6 g/dl) with negative viral PCR. Echocardiography excluded structural malformation. Cranial ultrasound showed diffuse edema without signs of hemorrhage or malformation. The ophthalmologic evaluation was normal. Laboratory findings showed elevated orthochromatic erythroblasts, persistent thrombocytopenia, coagulopathy, and severe hypoalbuminemia, treated with repeated platelet and fresh frozen plasma transfusions, along with continuous albumin infusion. Ammonium, lactate, and alpha-1 antitrypsin values were within the normal range, as was hemoglobin electrophoresis. Direct Coombs test on umbilical cord blood was negative. Serology and PCR were negative for TORCH and parvovirus B19. Routine neonatal metabolic screening was negative; specific tests for lactate storage disease, sialotransferrine isoelectrofocusing, and levels of acylcarnitine, lysosomal enzymes and mucopolysaccharides were normal. Radiographs excluded bone malformation or skeletal dysplasia. Hypotension and anuria appeared from the first hours of life, and repeated saline solution and diuretic boluses were administered without success. Cardiovascular support with vasoactive amines was given and in 48 hr his clinical condition progressively deteriorated with refractory hypotension, untreated acidosis, acute renal failure, hypo-oxygenation, with cardiovascular failure. Death occurred at 50 hr of life. Autopsy was declined by the family.

CGH-array did not reveal any gross genomic rearrangements. Based on the dysmorphic facial features, generalized hypotonia, and normal fetal growth, a tentative diagnosis of RASopathy was made, and screening of the first coding exon of SHOC2 identified the recurrent c.4A>G change (p.Ser2Gly) [Cordeddu et al., 2009]. Molecular screening of PTPN11, CRBL, SOS1, RAF1, HRAS, NRAS, KRAS, BRAF, MEK1, and MEK2 was performed by bidirectional Sanger sequencing of the entire coding sequence, thus ruling out concomitant functionally relevant mutations.

DISCUSSION
RASopathies are a group of conditions affecting growth and development caused by dysregulation of RAS signaling [Schubbert et al., 2007; Tidyman and Rauen, 2009; Tartaglia and Gelb, 2010]. Prenatal findings of NS, the most common among this family of disorders, include polyhydramnios, abnormal maternal serum triple screen, nuchal translucency >2.5 mm, distended jugular lymphatic sacs, posterior cervical hygroma, hydrops, anomalies like hydrothorax, congenital heart anomalies, and renal abnormalities at prenatal ultrasonography [Witt et al., 1987; Nisbet et al., 1999; Menashe et al., 2002; Bekker et al., 2007; Lee et al., 2009; Bakker et al., 2011; Baldassarre et al., 2011; Croonen et al., 2013]. In some cases, fetal hydrops and cystic hygroma have been reported to undergo spontaneous resolution after 36 weeks gestational [Izquierdo et al., 1990; Kiyota et al., 2008]. Consistent with these findings, mutations in PTPN11 occur in 2% of fetuses presenting increased nuchal translucency and in 16% with cystic hygroma [Lee et al., 2009]. A de novo mutation in either PTPN11, KRAS, or RAF1 was detected in 17.3% of fetuses with normal karyotype and abnormal ultrasound findings (increased nuchal translucency, distended jugular lymphatic sacs, hydrothorax, renal anomalies, polyhydramnios, cystic hygroma, cardiac anomalies, hydrops fetalis, and ascites) [Croonen et al., 2013].

While prenatal finding of abnormal triple test, increased nuchal translucency and congenital heart disease and postnatal diagnosis of hypertrophic myocardiopathy, pulmonic stenosis, ventricular septal defect, short stature, and myelodysplastic syndrome have been reported in a single subject with the c.4A>G SHOC2 mutation [Baldassarre et al., 2011], this is the first report documenting fetal hydrops and such a severe outcome associated with a mutated SHOC2 allele. This observation underlines the risk of such fetal...
anomalies at prenatal ultrasonography in NS/LAH. Hoban et al. [2012] reported a single NS/LAH case due to SHOC2 mutation which began with fetal distress requiring premature delivery at 32 weeks gestation. This patient, like the present one, showed dysmorphic features, edema, hepatosplenomegaly, leukocytosis, thrombocytopenia, and respiratory distress. The echocardiogram revealed hypertrophic cardiomyopathy with left ventricular outflow tract obstruction with an unfavorable outcome at 2 months. Early death is rare in NS/LAH, but in our case it was probably related to the severity of hydrops and hemodynamic impact. We can speculate whether birth at 30 weeks might have prevented hypertrophic cardiomyopathy from developing, and we do not know if hydrops would have improved with a longer pregnancy.

The most typical clinical features used to differentiate the RASopathies become evident later in infancy and are not so clear at birth [Digilio et al., 2011]. NS/LAH can be suspected in children with ectodermal features such as thin, slow-growing, easily pluckable, and sparse hair, characterized by an anagen stage of follicle development and bulbs lacking internal and external root sheats, keratosis pilaris, and pigmented skin [Mazzanti et al., 2003; Cordeddu et al., 2009]. These important clinical signs are not useful at birth because most newborn have thin hair and skin features of NS/LAH manifest later in childhood. The patient’s facial phenotype is consistent with a RASopathy in general, but it was difficult to suspect NS/LAH. A better definition of the phenotype in newborn may allow a faster clinical diagnosis, molecular confirmation, management, and genetic counseling for the families.

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