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Case Report Open Access

First Case of Congenital Myeloproliferative Disorder in a Newborn Diagnosed With Noonan Syndrome

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Abstract

Noonan syndrome (NS) is one of the most common genetic syndromes, but its diagnosis is difficult antenatally because prenatal ultrasound findings are unspecific. Infants with NS are predisposed to developing juvenile myelomonocytic leukaemia (JMML) or myeloproloferative disorders. We report a case of severe polyhydramnios and hydrops fetalis at 32+6 weeks gestation, complicated by preterm labour. Tocolysis, amnioreduction and pleuroamniotic shunt were performed. Fetal blood sampling showed: 1127 monocytes/mm^3 and 245 metamyelocytes/mm^3. The patient gave birth at 33 weeks and 4 days to a 2780 g male baby. Absolute monocyte count was maximum at 8000/mm^3, without blasts in peripheral blood. Study of the PTPN11 gene identified a de novo heterozygous missense mutation. Chemotherapy could not be started due to the severity of the multiple organ failure. The patient died at 2 months old. The prenatal monocytosis >1000/µL is one of the criteria for JMML. We suggest performing a cordocentesis, including white cell blood count in order to search for myelomonocytic disorders, especially in cases of hydropic fetuses and severe pleural effusions, before placing pleuroamniotic shunts. This could help evoking the diagnosis of NS and anticipating the postnatal clinical course.

Keywords: Noonan syndrome; Juvenile myelomonocytic leukaemia; Myeloproliferative disorde

Introduction

Noonan syndrome (NS, OMIM 163950) is one of the most common genetic syndromes manifesting at birth with an estimated prevalence of 1:1000 to 1:2500 live births. Diagnosis is difficult antenatally because prenatal ultrasound findings are unspecific. NS is transmitted as an autosomal dominant trait. Diagnosis of Noonan syndrome can be challenging because of the great variability in clinical presentation. The main characteristics are typical facial dysmorphism, growth retardation, congenital heart defect and developmental delay of variable severity [1]. A myeloproliferative disorder (MPD) can occasionally be diagnosed in infants with NS. The clinical course of NS with MPD is usually benign with spontaneous remission. However, certain cases have been described with an aggressive course, resembling juvenile myelomonocytic leukemia (JMML) [2]. JMML is a rare hematologic malignancy in children. Its presentations include anemia, thrombocytopenia, monocytosis, skin rash, marked hepatomegaly, and/or splenomegaly. Fever and respiratory involvement are common. We report a fatal case of Noonan syndrome in which a juvenile myelomonocytic leukemia was detected at 33 weeks gestation.

Case Report

A 28-year-old, gravida 6 para 2, was referred to our hospital because of preterm labour, related to polyhydramnios and hydrops fetalis at 32+6 weeks gestation.First trimester US revealed bilateral distended jugular lymphatic sacs (JLS) and the nuchal translucency was 2.8 mm. The second trimester maternal serum markers showed a risk at 1:525 for Down syndrome (AFP 1.39 MoM and HCG 2.98 MoM). Amniocentesis was performed and revealed a normal male karyotype. At 32+6 weeks the US scanning revealed severe polyhydramnios (maximal vertical pocket 19 cm), with severe bilateral pleural effusions, mild ascites, skin edema (Figure 1) and normal stomach. Tocolysis, antenatal corticosteroids, amnioreduction (3.6L and then 2.4L) and pleuroamniotic shunt were performed. Fetal blood sampling showed: haemoglobin=19.7 mg/dL, platelets 94. 109/L, reticulocytes 7.66%, erythroblasts 8.6%. The leukocytes were at 4.9. 109/L with 23% monocytes (1120/µL) and 5% metamyelocytes. No vacuoled lymphocytes were detected. Pleural puncture was characterized as chylothorax and showed no sign of metabolic disease. Finally, the patient presented a rupture of membranes with spontaneous labour and we performed a caesarean section because of breech position and persistant nuchal edema. The patient gave birth at 33 weeks and 4 days to a 2780 g (90th perc) preterm male, Apgar 5,8. His lenght was 42 cm (<15th perc) and head circumference 35 cm (>95th perc). We removed the 2 shunts immediately after birth and he was intubated with mecanichal ventilation for neonatal respitory distress. Postnatal outcome was poor with persistent multiple organ failure. Neonatal infection was eliminated in the first 48 hours. Mechanical ventilation was maintained during 2 months. Pleural effusion was resistant to octreotide and required pleural drainage. Histopathology showed a lymphothorax without abnormal cells. Anuric renal failure appeared at day 32 and required peritoneal dialysis from day 34 to day 61. Renal biopsy showed tubular necrosis and hematopoietic renal infiltration. Fever was observed without inflammatory syndrome (negative C

reactive protein) nor positive bacteriologic sample. Hepatomegaly was observed without hepatic function insuffiency.

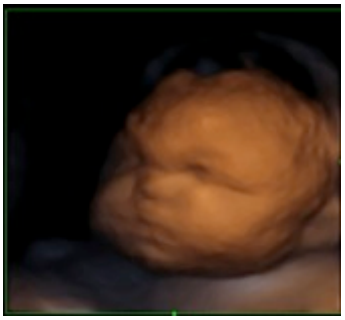

Figure1: 3D ultrasound: frontal edema

Noonan syndrome was suspected because of the facial characteristics (hypertelorism, downslanting palpebral fissures, low set, posteriorly rotated ears) typical cardiac anomalies (pulmonary valve stenosis and persistant ductus arteriosus) and pleural effusion. Evolution was complicated by juvenile myelomonocytic leukaemia. Absolute monocyte count was 3320/mm^3 at day 3 and maximum at 8000/mm^3 at day 16, without blasts in peripheral blood. The fetal haemoglobin was 59.9% at day 33. The immature myeloid precursors on a peripheral smear (CFU GM and CFU M) grew up spontaneously at day 46. Bone marrow aspiration was performed but was not contributive for diagnosis. Study of the PTPN11 gene identified a de novo heterozygous missense mutation, c.854T>C (p.Phe285Ser), in a blood sample. Chemotherapy was discussed but, due to the severity of the multiple organ failure, could not be started. The patient died of multiple organ failure at 2 months old. Necropsy showed an infiltration of CD15+, CD68+, CD34- and CD117- cells in the liver, stomach, skin and renal sinusoids and in the lymphatic tissues.

Discussion

As far as we are aware, this is the first report of a NS with myeloproliferative disorder of prenatal diagnosis. NS is transmitted as an autosomal dominant trait. In approximately 50% of the patients with a clinical diagnosis of NS, a heterozygous missense mutation is identified in the PTPN11 gene on chromosome 12 [1]. In PTPN11 negative NS patients, heterozygous missense mutations in other genes of the Ras-MAPK pathway can be found (SOS1, RAF1, KRAS, etc). Mutations occur de novo or can be inherited by an affected parent (in 30 to 75% of cases).

Diagnosis of NS can be challenging for sonographers as well as for pediatricians and geneticists, because of the great variability in clinical presentation. The main characteristics are typical facial dysmorphism, growth retardation, congenital heart defect, and developmental delay of variable severity. Main facial characteristics are hypertelorism, downslanting palpebral fissures, epicanthic fold, ptosis, low-set posteriorly rotated ears, and broad or webbed neck. The most common congenital heart defects are pulmonary valve stenosis and hypertrophic cardiomyopathy.

In a recent retrospective study of 28 cases of NS born between 1995 and 2011, Gaudineau et al. showed that the most frequent prenatal features – increased nuchal translucency, cystic hygroma and polyhydramnios – had a prevalence of 46%. They showed that diagnosis of NS tended to be earlier in cases involving prenatal ultrasound features, because of referral for a genetic consultation. Nevertheless, the presence of prenatal ultrasound features of NS did not seem to be correlated to its phenotypic evolution [3].

In a retrospective study on 47 patients, Baldassarre et al. [4] reviewed the prenatal findings in NS and correlated them with genotype and postnatal phenotype (criteria including age of clinical onset and severity of congenital heart disease, growth pattern, neuropsychomotor development electroencephalography anomalies and/or epilepsy, occurrence of haematological anomalies). They didn't find any statistical association between prenatal findings and neither NS genotype, nor scores of postnatal phenotype according to van der Burgt's criteria [5]. However, presence of morphological fetal anomalies at ultrasonography was associated with developmental delay/intellectual disabilities ($p<0.001$) and juvenile leukaemia ($p=0.006$). In their study, five patients (11%) presented haematological anomalies: juvenile myelomonocytic leukaemia (JMML) documented in four cases, and a myelodysplastic disorder in one, spontaneously resolved in all of them. Morphologic fetal US anomalies were more frequent in NS with haematologic disorders than the others NS. Specifically, three of them presented hydrothorax and the author found that this correlation between fetal multiple effusions and MPD intriguing and that it would require further analysis [4].

Bakker et al. [6] reported 3 cases (including one case with a monocytic reaction 2 weeks after birth) and a review of the literature of 39 cases. They recommend three-dimensional investigation focused on the nose, mouth, ears and profile of the fetus. Timeus et al. [7] reported 5 JMML in Noonan syndrome diagnosed early in childhood (10 days, 1 month and 2 months). They found that 2 of them had a high circulating CD34+ cell count. In our case, immunophenotypage showed CD34- cells but hypersensitivity to GM-CSF and spontaneous CFU-GM growth. Overall, Strullu et al. reported in 2014 a serie of 20 cases of patients with NS and JMML [8]. In this serie, all the patients presented PTPN11 mutation and JMML most often appeared in the neoanatal period, earlier than sporadic JMML. Life-threatening complications related to congenital heart defect, pleural effusion, leukaemia infiltrates and/or thrombocytopenia were noted in 12/20 (60%) of patients. Ten of these 12 patients died soon after diagnosis from haemodynamic failure, respiratory failure or cerebral haemorrhage.

Juvenile myelomonocytic leukemia and myeloproliferative disorders were also reported in NS infants [3,4,6,8,9] but not in fetuses.In our case, prenatal monocytosis >1000/L is one of the criteria for JMML [7,10]. The presence of immature blood cells can be found in cases of infection. In our case, infection was excluded after birth. Myelemia in fetal blood was also related to a congenital myeloproliferative disorder. Furthermore, prenatal US anomalies, mostly hydrothorax, were observed to correlate to an increased likelihood of myelodysplasic disorders and JMML [4]. In case of hydropic fetuses, cordocentesis may be performed for the diagnostic work-up (including haemoglogin level, search for vacuoled lymphocytes, fetal karyotyping, and search for viral infection) and for premedication (sufentanyl and curare injection) before placing pleuro-amniotic shunts. In such cases, the full blood count can reveal prenatal myeloproliferative disorders, acute leukemia or congenital transient leukemia. However it is the first time that myeloproliferative disorder is reported antenatally in a case of NS.

Ultrasound findings in fetuses with Noonan syndrome are unspecific and rarely lead to a prenatal diagnosis. Prenatal US

anomalies, mostly hydrothorax, were observed to be associated with an increased likelihood of juvenile myelomonocytic leukemia and myeloproliferative disorders. We suggest performing a fetal blood sampling, including a white cell blood count in order to search for myelomonocytic disorders, especially in cases of hydropic fetuses and severe pleural effusions, before placing pleuroamniotic shunts. This could help evoking the diagnosis of NS and above all, anticipating the postnatal clinical course.

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