Thoracic Hypoplasia at Birth as Presenting Feature of Shwachman-Diamond Syndrome in Twins

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Abstract

Keywords

- thoracic hypoplasia
- newborn
- neutropenia
- exocrine pancreatic dysfunction
- limb shortness

Shwachman-Diamond syndrome (SDS) is a rare autosomal recessive disorder of marrow failure syndrome and exocrine pancreatic dysfunction with an estimated incidence of 1/76,000. When present, characteristic skeletal abnormalities are strongly suggestive of SDS but most often they are seen during childhood and adolescence. We present a case of preterm twins with prenatal diagnosis of thoracic hypoplasia and a clinical evolution that lead to an early diagnosis of SDS. This report highlights the importance of a high index of suspicion for SDS in case of neonatal thoracic hypoplasia.

Introduction

Shwachman-Diamond syndrome (SDS) is a rare autosomal recessive disorder characterized by marrow failure syndrome and exocrine pancreatic dysfunction with an estimated incidence of 1/76,000.¹ Pancreatic dysfunction is usually diagnosed during the first-year of life for occurrence of failure to thrive but haematological problems can be intermittent so the diagnosis is not always immediately obvious. When present, characteristic skeletal abnormalities are strongly suggestive of SDS but most often they are seen during childhood and adolescence. Consequently, clinical diagnosis is generally made in the first year of life, although occasionally, the diagnosis may be established in older children and even adults.^{2,3}

More than 90% of the SDS patients have alterations in chromosome 7, the *SBDS* gene (named after Shwachman–Bodian–Diamond), located on 7q11, that is predicted to code for a 250 amino acid protein of (currently) unknown function. The transcript of the normal gene is widely expressed in the pancreas, bone marrow, and leucocytes; and it is assumed to be necessary for the normal development of these tissues.² In recent years, DNA analysis may lead to the diagnosis of SDS before the full clinical spectrum appears, resulting in improved health care of patients affected through a multidisciplinary program for prevention and therapy of clinical features.

This case report indicates that SDS should be in the differential diagnosis of thoracic hypoplasia at birth.

Case Report

Three preterm male twins (GA 33 wk +5/7) from spontaneous gestation were transferred to our neonatal intensive care unit because of prematurity, low birth weight, respiratory distress at birth, and suspicion of osteodysplasia for two of them. They were born via caesarean section from nonconsanguineous healthy parents. A previous child of the couple was in good health. A prenatal ultrasonography performed at 20 weeks of gestation showed two monochorionic diamniotic fetuses with early harmonic intrauterine growth restriction, thorax hypoplasia, limb shortness, hyperechogenic bowel, and suspicion of osteodysplasia. The monochorionic monoamniotic fetus had no anomalies.

Birth weight was 1.310 kg (<5th percentile), length 41 cm (5th percentile), head circumference 28.5 cm (<5th percentile) for the first newborn (Twin 1); birth weight was 1.350 kg (<5th percentile), length 40.5 cm (<5th percentile), head circumference 28 cm (<5th percentile) for the second one (Twin 2), and birth weight was 1.970 kg (5th–10th percentile), length 41.5 cm (5th–10th percentile), head circumference 29 cm (5th percentile) for the third one. The latter had good clinical course, with a normal recovery of

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weight, length, and head circumference, and was discharged home rapidly.

In both Twin 1 and 2 respiratory distress syndrome, thorax hypoplasia, and limb shortness were evident from birth.

Twin 2 showed, during the hospital stay, intermittent neutropenia (minimum neutrophils $220/\text{mm}^3$), and persistent significant thrombocytopenia (minimum platelets $8,000/\text{mm}^3$), both starting in the first days. Complete blood count in first days of life was white cells $7,660/\text{mm}^3$ (neutrophils 430, lymphocyte 6,680, monocyte 240, eosinophils 20, basophils 40), erythrocytes $4,380,000/\text{mm}^3$, hemoglobin 14.3 g/dL, and platelets $31,000/\text{mm}^3$. Thrombocytopenia was unresponsive to immunoglobulins and steroid treatment. Neutropenia was unresponsive to granulocyte-colony stimulating factor (G-CSF) treatment. Antibodies against neutrophils and platelets in neonate and parents were negative in direct and indirect test. During hospital stay, he also showed erythropoietin refractory anemia. Twelve platelet transfusions and eight blood transfusions were needed during the hospital stay. Twin 2 had patent ductus arteriosus, bronchopulmonary dysplasia, and pulmonary hypertension treated with sildenafil.

Radiographs in both twins confirmed a hypoplastic chest, characterized by reduction of chest diameter, and a shorter tibia compared to fibula (►Fig. 1). Genetic consult initially suspected both twins being affected by asphyxiating thoracic dystrophy (ATD, Jeune syndrome).

Considering the significant and persistent thrombocytopenia in Twin 2, a peripheral blood smear was performed, showing erythrocyte anisocytosis, leucopenia with neutropenia, and low platelet count. Bone marrow aspiration showed reduced cellularity with poor erythroid series, myeloid series stopped at myelocyte status, and absence of megakaryocytes.

Fig. 1 X rays of twin 1 showing hypoplastic chest characterized by reduction of chest diameters.

Twin 1 developed seborrheic dermatitis and severe failure to thrive that induced us to investigate for malabsorption. Twin 1 showed steatorrhea (fecal fat analysis, 16%) and very low level of fecal elastase (fecal elastase, 9 with normal value > 200) diagnostic for pancreatic exocrine failure. He didn't show significant thrombocytopenia and neutropenia. Twin 1 required much less blood and platelet transfusion compared to Twin 2, except in the final period of life consequently to very serious clinical deterioration.

Thus putting together the features from both twins: marrow failure in Twin 2 and exocrine pancreatic dysfunction in Twin 1 plus the presence of skeletal malformation, Shwachman-Diamond syndrome (SDS) was suspected. The diagnosis was confirmed by sequence analysis for *SBDS* gene on chromosome 7 revealing the compound heterozygous mutations c.258 + 2T > C and c.107delT. Testing of parental DNA confirmed that one mutated allele was inherited from each parent. Meanwhile, an abdomen echography confirmed pancreatic lipomatosis in Twin 1; sweat test was normal as were calcium-phosphorus metabolism, karyotype, and ophthalmological examination for both twins.

Both twins needed respiratory support throughout their hospital stay. They received supportive care with blood and platelets transfusions, G-CSF, and immunoglobulins infusions. They had repeated episodes of clinical sepsis (clinical deterioration, increased C-reactive protein with blood cultures always negative), and pneumonia (*Klebsiella pneumoniae* and multidrug resistant *Stenotrophomonas maltophilia* were isolated in several tracheal aspirate cultures) treated with antibiotics. Severe respiratory distress resulted in death on the 133rd day of life for Twin 2, and on the 173rd day of life for Twin 1. Parents received a genetic consult in which they were recommended to perform DNA analysis for *SBDS* gene in Twin 3 and in the first son of the couple. Also, the family pediatrician was informed on the diagnosis of SDS for twin 1 and 2.

Discussion

The differential diagnosis of a neonate with thoracic hypoplasia includes a range of rare syndromes: (ATD, Ellis-van Creveld syndrome, short rib-polydactyly syndrome (type I-IV), thoracolumbar dysplasia (Barnes syndrome), and SDS.⁴

Although ATD is an important potential diagnosis in case of neonatal respiratory distress and thoracic hypoplasia, there are some cases in literature that report ATD misdiagnosis in children later diagnosed as SDS.⁴⁻⁸

SDS is a rare autosomal recessive disorder first described in 1964; it is a multisystem disease involving bone marrow, pancreas, bony skeleton, and other organs such as liver, kidneys, teeth, brain, immune system; and is also associated with myelodysplastic syndrome and leukemia.^{2,9} It is caused by mutations in the gene encoding Shwachman-Bodian-Diamond syndrome protein (*SBDS*), which is involved in several pathways that deal with ribosomal RNA metabolism, apoptosis, and mitotic spindle stabilization.¹⁰⁻¹²

The predominant manifestations of SDS include bone marrow failure, pancreatic exocrine dysfunction, and skeletal

abnormalities. In SDS, rib and/or thoracic cage abnormalities, including shortened ribs with flared ends and costochondral thickening, can occur in 30 to 50% of patients, although they typically develop later in childhood.

All clinical features of SDS may develop throughout childhood and adolescence. Consequently, clinical diagnosis is generally made in children, and sometimes even in adults. Early diagnosis of SDS is a challenge, especially in the neonatal period. An early diagnosis of SDS may improve health care of patients affected through a multidisciplinary program for prevention and treatment of clinical features of such disease. The benefits of early SDS diagnosis allows a more specific and aggressive management of marrow and pancreatic dysfunction, and skeletal disease, to improve outcomes. These include a timely initiation of an appropriate program to correct malnutrition, prevent and correct limb deformities and osteoporosis, and to detect evolving marrow abnormalities such as severe marrow failure, myelodysplastic syndrome or leukemia.

Our report shows two atypical cases of SDS in which a very early diagnosis has been made in neonatal period. The skeletal involvement was the predominant and first manifestation since the foetal ultrasound. Adding the features from both twins, marrow failure in one twin and exocrine pancreatic dysfunction in the other, together with thoracic hypoplasia, gave rise to the suspicion of SDS confirmed by DNA analysis.

After birth, thoracic hypoplasia with respiratory distress syndrome might lead to a diagnosis of the equally rare ATD (incidence 1:100,000–130,000).⁴ The systemic involvement described in some cases of ATD that can include hepatic fibrosis, renal failure, and rarely pancreatic fibrosis¹³ makes the diagnostic process difficult. In the literature, at least four cases of an ATD diagnosis in a patient with likely SDS are reported: the first case described in 1973 presented two siblings with thoracic hypoplasia at birth who were diagnosed as affected by ATD, one of them developed pancreatic insufficiency⁶; in 1976 two sets of siblings with metaphyseal chondrodysplasia, neutropenia, and pancreatic insufficiency with respiratory distress in the neonatal period were reported.⁷ Given the clinical features, the diagnosis of SDS in these cases was very likely, even if testing for the *SBDS* gene was not available at that time. A recent paper reports another case of suspected ATD at birth, then reclassified as SDS when the classical clinical triade appeared over the years and confirmed by genetic testing.⁴ Pancreatic exocrine failure and imaging with the evidence of pancreatic lipomatosis is helpful for the early diagnosis. However, DNA analysis has the final word to confirm the diagnostic suspicion, although, about 10% of cases have no identified mutations.² For the latter cases, a careful follow-up is mandatory because in SDS, pancreatic and marrow dysfunctions may manifest at a later age. Also, in case of SDS, genetic counseling for the family and evaluation of asymptomatic siblings needs to be done.¹⁴

This report underlines how in case of thoracic hypoplasia at birth, it is necessary to consider SDS as a possible diagnosis. Searching for exocrine pancreatic insufficiency and bone marrow failure together with accurate pancreatic imaging may help in diagnosis. *SBDS* genotyping should always be performed for confirmation.

Conflict of Interest

None.

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