REVIEW

Shwachman Diamond Syndrome: an emergency challenge

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ABSTRACT

Shwachman Diamond Syndrome is a rare congenital disorder characterized by pancreatic insufficiency, bone marrow dysfunction and skeletal abnormalities. No specific test is available for a definitive diagnosis for SDS. In the presence of clinical features of SDS, pancreatic insufficiency should be tested for or lipomatosis radiologically demonstrated. New directions might be found in genetic analysis. Sometimes, a life-threatening event may be the first clinical manifestation of the syndrome.

Keywords: lipomatosis, SDS, diagnosis, children

Shwachman Diamond Syndrome: a diagnostic challenge.

Shwachman Diamond syndrome (SDS) is a congenital disorder, first described in 1964 in five patients showing exocrine pancreatic insufficiency and leucopenia. (1)

Although SDS is a rare disorder, it is the most common cause of pancreatic insufficiency in children next to cystic fibrosis and probably the third most common inherited bone marrow failure syndrome after Fanconi's anemia and Diamond-Blackfan anemia.

An autosomal recessive mode of inheritance has been described.

Up to December 2000, more than 300 cases of SDS had been reported in the literature. (2)

Clinical features

SDS usually manifests itself in infancy with multisystemic abnormalities including exocrine pancreatic insufficiency, hematological and skeletal abnormalities. The clinical phenotype of SDS is extremely heterogeneous. (3,4) No unifying pathogenetic mechanism has yet been shown to be responsible for SDS, although new insights into molecular, genetic and cellular basis of this rare disease have recently been described. (3)

Pancreatic insufficiency. Histological analysis of the pancreas shows preserved ducts and paucity of acini with fatty replacement in the gland. More than 98% of the exocrine acinar capacity of the pancreas must be lost before the clinical symptoms of pancreatic insufficiency appear. Steatorrhea is noted in the first 6 months of life in about 50% of affected children and increases to 90% by the age of one. (5) Steatorrhea and malabsorption might lead to malnutrition and fat-soluble vitamin deficiency (A, D, E, K). (4)

Hematological abnormalities. Inter-

mittent neutropenia is the most common hematological finding in SDS, occurring in 88-100% of patients and it can be persistently or intermittently severe, with a neutrophil count of $<0.5\text{x}10^9$/L. (6) The neutrophils in patients affected with SDS may have impaired mobility and defects in migration or chemotaxis. (5) Alterations in neutrophil cytoskeletal/microtubular integrity and function may play a significant role in causing the defective chemotaxis.

Therefore, more of the bone marrow cellular elements can be involved. Hematological manifestations other than neutropenia include anemia, raised fetal hemoglobin levels, thrombocytopenia and aplastic anemia. Anemia is the second most common cytopenia in SDS, recorded in up to 80% of patients. It is usually mild and normochromic-normocytic with a low reticulocyte count. (2) Fetal hemoglobin was increased in 80% of patients. (7)

Many patients develop a mild and clinically insignificant thrombocyto-

penia, defined by a platelet count < 150×10^9/L.

Pancytopenia occurs in 10-65% of patients. Both anemia and thrombocytopenia are usually mild to moderate in these cases but neutropenia tends to be severe. Trilineage cytopenia is associated with a poor prognosis, that is, a higher probability of developing symptomatic severe aplasia. (8) Hemopoiesis is probably affected by defects in the marrow-stromal support structure. (2)

As with other constitutional bone marrow failure syndromes, retrospective studies suggested a high propensity for malignant transformation into myelodysplastic syndromes and acute myeloid leukemia (25-33% of the patients). The detection of cytogenetic abnormalities in the bone marrow is a marker of clonal evolution and malignant transformation. (2) The isochromosome 7q (i7q) was found with malignant myeloid transformation in 25% of SDS patients. (2,9,10)

Skeletal abnormalities. The musculoskeletal system is the most commonly affected organ after the hematopoietic and pancreatic systems; more than half of SDS patients have metaphyseal dysostoses, which usually involves the femoral head. Radiographs may detect these alterations after 12 months of age. Approximately 30-50% of patients show thoracic cage defects, including shortened ribs with flared ends and chostocondral thickening. (11) Other skeletal problems include syndactyly, clinodactyly, supernumerary thumbs, kyphosis and scoliosis. (12) Significant osteoporosis and osteomalacia are often observed, most likely due to a decrease in vitamin D and vitamin K absorption, which result in a high risk of pathological fractures. (11)

Immune dysfunction. Patients with SDS experience recurrent viral, bacterial and fungal infections, including otitis media, bronchopneumonia, osteomyelitis, skin infection and septicemia. The quantitative and qualitative defects in SDS neutrophils contribute to these infections. Various defects in B and T cells have been reported, both quantitative (low IgG levels, low percentage of circulating B lymphocytes) and qualitative (decreased in vitro lymphocyte proliferation, lack of specific antibody production). (13)

Other involvement. Failure to thrive is commonly observed in patients affected with SDS and various factors may contribute to this condition, including malabsorption, recurrent infections and metaphyseal dysostoses. Birth weight is often normal, but more than 50% of patients are still below the 3rd percentile for height when they are one year old. (8) All patients exhibit delayed bone age and delayed puberty. Increased risk of caries, mucositis and periodontal infections, dental dysplasia and delayed dentition of permanent teeth are frequently seen. (14)

Hepatomegaly and raised liver enzymes are observed in 50-75%, especially in young children. (2)

Severe eczema is often seen at presentation. (15)

Recent studies suggest that cognitive and attention difficulties are experienced by a large number of affected children. (16)

Diagnosis

The clinical phenotype of SDS is extremely heterogeneous showing a wide range of abnormalities and symptoms. At present, no specific biochemical or genetic test is available for a definitive diagnosis for SDS. Based on current knowledge of the SDS phenotype, the diagnosis requires evidence of exocrine pancreatic dysfunction and characteristic hematological abnormalities. Short stature, skeletal abnormalities, hepatomegaly or biochemical abnormalities of the liver are supportive findings of the diagnosis. Clinical diagnostic criteria used by Dror and Freedman are listed in table 1. (2) Therefore, SDS must be suspected when neutropenia and recurrent infections are present, in all children with delayed growth, short stature, skeletal abnormalities or steatorrhea.

The recognition of pancreatic dysfunction has been regarded as an essential part of the diagnosis of SDS. Typically, exocrine enzyme secretion is diminished. The function of the exocrine pancreas is difficult to assess because of its anatomical inaccessibility and large reserve capacity. The "gold standard", the direct pancreatic stimulation test provides quantitative and accurate measures of pancreatic function but is not widely used in clinical practice because of its complexity, cost and invasiveness. Pancreatic insufficiency is assessed by the absence or decrease of trypsin, lipase and amylase activity in pancreatic fluid, sampled through a nasogastric tube, from less than 2% to approximately 10-14% of the reference range after a quantitative stimulation

Table 1: Diagnostic criteria for SDS.

Exocrine pancreatic dysfunction (at least one of the following):
• Abnormal quantitative pancreatic stimulation test.
• Serum cationic trypsinogen below the normal range.
• Abnormal 72 hour fecal fat analysis plus evidence of pancreatic lipomatosis by ultrasonographic examination or CT scan.

AND Hematological abnormalities (at least one of the following):
• Chronic (on two occasions at least 6 weeks apart) single lineage or multilineage cytopenia with bone marrow findings consistent with a productive defect:
    - neutrophil < 1.5×10^9/l
    - hemoglobin concentration <2 standard deviations below mean, adjusted for age
    - thrombocytopenia <150×10^9/l.
• Myelodysplastic syndrome.

test with intravenous secretin and cholecystokinin. (2)

In SDS, low serum immunoreactive trypsinogen values are based on reduced acinar enzyme production, because pancreatic failure is due to hypoplasia. On the other hand, in cystic fibrosis, the serum immunoreactive trypsinogen level is high because of the underlying pathophysiological features affecting the pancreatic duct and the inability to secrete digestive enzymes into the duodenal lumen.

In some patients with SDS, the exocrine pancreatic enzyme production is so low that the patient clinically manifests with steatorrhea and has abnormal 72-hour fecal fat studies. However, the absence of steatorrhea does not exclude the diagnosis of SDS. (8)

Syndromes that can manifest pancreatic pathology include: Beckwith Wiedemann syndrome, von Hippel-Lindau disease, autosomal dominant polycystic kidney disease and Pearson disease (pancreatic insufficiency, neutropenia, marrow ring sideroblasts and vacuolated erythroid and myeloid precursors). Pancreatic abnormalities, associated with fatty replacement of the gland, can be found also in cystic fibrosis, Cushing syndrome, obesity or Johanson Blizzard Syndrome. (17)

A negative sweat test allows us to rule out the diagnosis of cystic fibrosis.

Histological analysis of the pancreas shows preserved ducts and paucity of acinis with fatty replacement in the gland, a feature that may be delineated by appropriate radiological imaging studies.

Pancreatic lipomatosis is a radiological feature of SDS as well as of the very rare Johanson Blizzard Syndrome but other clinical abnormalities (facial and especially urogenital) should help to differentiate the two entities.

Diagnostic imaging plays a mayor role in the evaluation of the pancreas in infants and children. (18)

Ultrasonography represents the less invasive radiological technique for investigating the pancreatic gland. The pancreas, in SDS affected patients, appears of normal size with increased echogenicity of the silhouette. In contrast, the size of the pancreas in patients with cystic fibrosis usually is decreased. However, ultrasonography might be inadequate as the size of the gland cannot be easily measured with accuracy for its hyperechogenicity or for the presence of abdominal meteorism due to malabsorption.

CT and MRI reveal lipomatosis of the pancreas with greater accuracy but CT has the major disadvantage of using ionizing radiation.

MRI is an imaging method that allows correlation of the tissue specificity of an organ to its radiological representation, especially in the presence of fat, which is easily recognized in T1 and T2 weighted sequences. (19)

Therefore, when pancreatic lipomatosis assessed by MRI, or CT, is associated with clinical characteristics which are suggestive of SDS, diagnosis of SDS should be strongly considered.

Genetic analysis

In 2002, researchers from Toronto cloned the gene responsible for SDS (SBDS) and identified mutations involved in the disease. The gene has been mapped to chromosome 7q11. Molecular diagnostic testing is now available. (5) The SBDS gene mutations have been detected in most (80%), but not all patients with SDS. (20) This suggests that SDS is a genetically heterogeneous disorder. The SBDS gene has an adjacent pseudogene (an identical but nonfunctional gene) on 7q11. The majority of mutations are caused by a recombination during meiosis between SBDS and its highly homologous pseudogene, so that some parts of the pseudogene are incorporated into the normal SBDS gene. The altered SBDS gene received non functional parts from the pseudogene, which made it dysfunctional. (5)

The function of the SBDS encoded protein has not been elucidated. The transcript of the normal gene is widely expressed in the pancreas, bone marrow and leucocytes. Hence, it has been postulated that the SDS phenotype may result from a defect in RNA processing that disrupts a cellular function necessary for hematopoietic, pancreatic and skeletal development. (21)

Acute manifestations and supportive care

Overwhelming sepsis is a well recognized fatal complication of this disorder, particularly early in life. (2) In case of fever and severe neutropenia, bacterial cultures (from blood, urine, throat) should be performed because of the increased risk of sepsis from the neutrophil migrational defect observed in the disease. In addition, patients should receive prompt therapy based on intravenous antibiotics with a broad spectrum coverage until the infection clears up. Granulocyte colony stimulating factor (G-CSF) may be prescribed and patients would probably benefit during acute infections. (2) The most likely bacterial pathogens in SDS are Staphylococcus Aureus, Haemophilus influenzae and Pseudomonas species. (22)

Fatal bleeding, in patients suffering from moderate to severe thrombocytopenia, has been reported. (9) Platelet and/or plasma transfusions and parenteral vitamin K may be necessary to diminish the risk of bleeding. Although patients with anemia and thrombocytopenia may be supported by red cell and platelet transfusions, very severe neutropenia (ANC < 200/μL) remains an adverse prognostic factor as it is associated with a high mortality rate and risk of life-threatening infections. (23)

Natural history

Prognosis is uncertain. Since SDS has been described relatively recently, limited data are available regarding follow up in these affected patients. Death usually occurs from overwhelming sepsis or malignancies. Alter et al (1997) reported a median survival age older than 35 years for all patients with SDS. For those patients whose course is complicated by aplastic anemia, the median survival age is 24 years, while those patients whose course is complicated by leukemia have a median survival age of 10 years. (24)

Management

Management of children with SDS should be multidisciplinary. The child should be primarily under the care of a local general pediatrician. Long term follow up requires collaboration between pediatric gastroenterologists and hematologists. A significant proportion of patients with SDS require pancreatic enzymes. The dosage should be adapted to the severity of the symptoms, such as steatorrhea, abdominal pain and growth parameters.

Depending on the evolution of hematological abnormalities, a full blood count must be performed every 3-6 months or more frequently if symptoms require. An annual bone marrow biopsy has to be performed for surveillance of the acquisition of cytogenetic abnormalities. (5)

Complications of the disease, such as sepsis or hematological symptomatic abnormalities, might require admission to an Intensive Care Unit.

Conclusion

Any child with steatorrhea and poor weight gain, after excluding cystic fibrosis, should be investigated for exocrine pancreatic insufficiency. The assessment of pancreatic dysfunction or the less invasive radiological demonstration of fatty replacement has primary importance. Diagnostic criteria should help in establishing the diagnosis. Other clinical abnormalities support the suspected condition. A specific diag-nostic test for SDS is not available and definitive diagnosis still represents a challenge. Genetic analysis might be the future direction. Clinicians should take into account that life-threatening events may be the first clinical manifestation of the disease.

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