

Case Report

Schwachman-Diamond Syndrome in a Child with Severe Failure to Thrive and Gastrointestinal Symptoms, in Pakistan – A Case Report

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- Genetic disorders
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Abstract

Shwachman-Diamond syndrome (SDS), is an autosomal recessive multi-organ genetic disorder characterized mainly by exocrine pancreatic insufficiency, skeletal abnormalities and hematological abnormalities due to bone marrow dysfunction. It is a rare condition with only a few hundred cases reported. Herein, we report a case of SDS for the first time in Pakistan. Our patient, a 2-year old male child, presented with a chronic history of severe failure to thrive, diarrhea and vomiting. After undergoing extensive evaluation and testing, he was eventually diagnosed as a case of SDS. Elaborate clinical features and details pertaining to the diagnostic process and management are described.

INTRODUCTION

Shwachman-Diamond syndrome (SDS), is a rare multi-organ, autosomal recessive genetic disorder with only a few hundred cases reported. More than 90% of cases are caused by compound heterozygous or homozygous *Shwachman-Bodian-Diamond syndrome (SBDS)* gene mutations on chromosome 7q11 [1]. Its clinical presentation mainly comprises pancreatic exocrine insufficiency, skeletal abnormalities, and hematological abnormalities due to bone marrow dysfunction, possibly leading to a higher risk for malignant transformation [2]. Other common features of SDS include diarrhea, failure to thrive in infancy, elevation in fetal hemoglobin, anemia, neutropenia associated with bone marrow hypoplasia, and normal sweat electrolytes [3]. Rarely, immunological and cardiac abnormalities have been reported as well [4]. Herein, we report a case of SDS for the first time in Pakistan. The patient presented with severe failure to thrive alongside chronic diarrhea and vomiting.

CASE PRESENTATION

General information

A 2 year old male child presented to the Out-Patient Department of Liaquat National Hospital, Karachi, Pakistan, with complaints of severe failure to thrive and unexplained diarrhea since birth. He had food intolerance and on-off vomiting for the past 1 year. He was delivered on term through a C-section due

to meconium aspiration, but did not require intensive care. His birth weight was 2.6kg [5th Percentile]. There were no other complications during or after pregnancy. He was a result of non-consanguineous marriage. He reached all developmental milestones timely. The baby started passing loose stools as soon as he started feeding. The loose stools started off as 3-5 episodes per day but gradually progressed to 20-25 episodes per day. They were watery in consistency and variable in color. All lab tests were normal and didn't show signs of infection or any underlying pathology. At 1 year of age, the child started vomiting, which started off as 1-2 episodes per day, but progressed to 3-4 episodes per day. The vomiting was usually spontaneous but was often associated with food intake. At the time of presentation, he looked wasted and was very irritable. His height was normal at 84cm but weight was 8kg, indicating severe failure to thrive. He had maxillary prominence and peg shaped teeth with poor enamel (Figure 1). There was no hepatomegaly, splenomegaly or localized or generalized lymphadenopathy. His behavior, appetite and sleep habits had been disturbed for the entire duration. He had an extremely poor oral food intake on account of his vomiting. There were no urinary or respiratory complaints. He had an elaborate work-up to rule out malnutrition, tuberculosis, cystic fibrosis, celiac disease and infections. Eventually, he was tested positive for stool elastase deficiency which in combination of skeletal and hematological abnormalities led to the diagnosis of SDS (Table 1).



Figure 1 Enlarged maxillary prominences, possibly pointing towards extramedullary hematopoiesis.

Table 1: Laboratory test results at presentation.

Section 1: Complete Blood Count (CBC) at presentation	
TEST	RESULT
HEMOGLOBIN	10.6g/dl
HEMATOCRIT	34%
R.B.C	3.1x10 ¹² /L
MCV	111fL
MCHC	31g/dL
WBC	8.3x10 ⁹ /L
NEUTROPHILS	25%
LYMPHOCYTES	71%
EOSINOPHILS	0%
MONOCYTES	4%
NLR	0.35
PLATELETS	479x10 ⁹
Section 2: Liver Function Tests (LFTs) at presentation	
TEST	RESULT
SERUM TOTAL BILIRUBIN	0.86 mg/dl
SERUM DIRECT BILIRUBIN	0.42 mg/dl
SERUM INDIRECT BILIRUBIN	0.44 mg/dl
SGPT (ALT)	29 U/l
ALP	154 U/l
GGT	33 U/l
SGOT (AST)	54 U/l
Section 3: Serum Electrolytes at presentation	
TEST	RESULT
SODIUM	132 mEq/l
POTASSIUM	3.4 mEq/l
CHLORIDE	106 mEq/l
BICARBONATE	19.7 mEq/l
Section 4: Other lab results	
TEST	RESULT
ANTI-TTG IgG (ELISA)	3.21 - NEGATIVE
CREATININE	0.30 mg/dl (Normal range 0.9-1.3)
UREA	10.7 mg/dl (Normal range 17-49)
SWEAT TEST	23 mmol/l (NEGATIVE)
PANCREATIC ELASTASE	75 ug/ml (normal range >200)

TREATMENT

After confirmed diagnosis, the patient underwent a percutaneous endoscopic gastrostomy (PEG), procedure for medication and feeding on account of his poor oral food intake, chronic history of vomiting and failure to thrive. Furthermore, the patient was administered Pancreatic enzyme replacement as 1000 units prior to every meal 3 times a day along with fat-soluble vitamin supplementation (vitamins A,D,E,K) 1ml daily and iron supplementation (iron polymaltose drops) once daily.

DISCUSSION

SDS is a rare autosomal recessive hereditary condition, with 90% of the patients having changes in the SBDS quality on chromosome 7q11; the most widely known mutations are c.258+2T> C and c.183-184TA> CT [2,5], which makes the SBDS protein truncated. The SBDS gene is responsible for synthesis of various proteins liable for microtubule stabilization and actin polymerization, additionally known to play part in bone marrow proliferation, mitosis and the matrix microenvironment [6]. Our patient could not undergo genetic testing due to unavailability of the test at the health facility and financial limitations on account of the patient.

SDS is a diverse disorder involving multiple organs, mainly the pancreas, liver, bones, blood system, immune system and teeth, and some less common associations include skin disorders. The main clinical manifestations involve pancreatic exocrine insufficiency, hematological abnormalities and skeletal deformities, usually occurring in infants and young children [6]. Table 1 shows drastic hematological changes in our patient over a period of 5 months. He developed a macrocytic anemia as evident by his low hemoglobin levels, low hematocrit, low RBC levels and high MCV. He also developed moderate to severe neutropenia and lymphocytosis (Table 1: Section 1).

SDS is the second most common cause of pancreatic insufficiency after cystic fibrosis. Therefore, considering the pancreatic dysfunction is of great importance in ruling out other differentials. Table 1 (Section 4), shows a negative sweat test in our patient, ruling out cystic fibrosis. Celiac disease was also ruled out with a negative ANTI-TTG IgG (ELISA) test (Table 1: Section 4). A normal metabolic profile further ruled out causes of malnutrition and malabsorption. SDS presents with exocrine pancreatic insufficiency in infants usually in the primary year of life. About 15% of the patients show signs of hepatomegaly, which may be due to fat deposition as well, hence a 'fatty liver'. Furthermore, 60% of the patients have shown elevated liver enzymes (transaminases) [4]. The main presenting manifestations to confirm diagnosis include decreased pancreatic elastase levels, decline in fat soluble vitamin content (A,D,E,K), and increasing fecal fatty content (steatorrhea), all of which indicate severe pancreatic dysfunction. Our patient was diagnosed with SDS on account of his severely low pancreatic elastase levels (Table 1: Section 4), inevitably pointing towards severe pancreatic insufficiency. This resulted in a fat-soluble vitamin deficiency as well, further contributing to his failure to thrive.

Monitoring the levels of fat soluble vitamins and vitamin K dependent prothrombin time in patients with untreated pancreatic insufficiency holds great importance for excluding

other differentials because some studies have shown resolution of hepatic symptoms like hepatomegaly and elevated transaminases by the age of 5 in SDS patients [2,7]. Our patient had mildly elevated AST and ALP levels, but ALT levels were normal, indicating mild hepatic dysfunction (Table 1: Section 2). Skeletal abnormalities are also common in SDS patients, such as stunted growth, spondylolithiasis, Spinal and thoracic abnormalities etc., all of which may occur secondary to malabsorption of vitamin D and K which require pancreatic juice for absorption, resulting in increased risks of getting fractures in extremities and spine [5]. Our patient showed tooth enamel defects, including hypomaturation, dental hypoplasia and dysplasia, and hypocalcification (Figure 1). He also had enlarged maxillary prominences, possibly pointing towards extramedullary hematopoiesis. There were no other skeletal abnormalities found.

A few cases additionally show critical neurological changes, these patients have extreme intellectual and behavioral disabilities which render huge hindrances to academic performance, intellectual reasoning, advanced verbal skills and visual motor skills [2]. Along with some structural changes as well, brain MRI of SDS patients with neurological deficits have shown reluctance with smaller posterior fossa and associated structures like corpus callosum, brain stem, and cerebellar vermis [8]. Our patient, however, did not show any signs of neurological impairment.

DECLARATIONS

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