A Case of Shwachman–Diamond Syndrome who Presented with Hypotonia

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Abstract

Keywords

- Shwachman–Diamond syndrome
- hypotonia
- SBDS gene
- compound heterozygous

We present a patient with failure to thrive and severe hypotonia, who was initially suspected of having a neurometabolic disease but later diagnosed as Shwachman–Diamond syndrome (SDS), which was genetically confirmed. SDS is a multisystemic disease, which is characterized by exocrine pancreatic deficiency, bone marrow dysfunction with increased risk for malignant transformation, and skeletal abnormalities. It should be included in differential diagnosis of patients with failure to thrive and unexplained neurodevelopmental delay with neutropenia.

Introduction

Shwachman–Diamond syndrome (SDS) is an autosomal recessive disease, which results from mutations in the SBDS gene at chromosome 7q11. It is characterized by exocrine pancreatic deficiency, bone marrow dysfunction with increased risk for malignant transformation, and skeletal abnormalities.¹

Herein, we present a patient with failure to thrive and severe hypotonia, who was initially suspected of having a neurometabolic disease but later diagnosed as SDS, which was genetically confirmed.

Case

An 8-month-old girl was referred to our hospital with complaints of developmental delay and diarrhea. She was the third child of healthy and unrelated parents, born at 37th week gestation with a birth weight of 2,440 g. She had two healthy elder sisters. She had frequent mucoid stools from birth while she was breastfed. Her stool frequency increased

with the introduction of complementary foods at the age of 6 months.

At the time of admission, our patient's height was 59 cm, weight was 5,300 g, and head circumference was 42 cm. All of them were below the 3rd percentile. Her liver was palpable 1 cm below the right costal margin. There was no splenomegaly and lymphadenopathy. She was floppy with a frog-legged posture and unable to control her head. Her deep tendon reflexes were normal and no fasciculations were detected on the tongue.

Laboratory investigation revealed hemoglobin, 13.4 g/L; leukocyte, $8.8 \times 10^9/L$; and platelet, $388 \times 10^9/L$. Mean corpuscular volume was 91.8 fl. The absolute neutrophil count was $0.86 \times 10^9/L$ indicating neutropenia. Peripheral blood smear yielded 80% of lymphocytes, 9% of dysmorphic monocytes, 9% neutrophils, 1% eosinophils, and 1% basophils. Her aspartate aminotransferase (182 IU/L), alanine aminotransferase (92 IU/L), and G-glutamyltransferase (51 IU/L) were elevated. Prothrombin time, albumin levels, creatine kinase, and other serum biochemical parameters were within the normal range. Tests for hepatitis A, B, and C viruses, human

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immunodeficiency virus, Epstein–Barr virus, and cytomegalovirus were negative. Toxoplasmosis, rubella, cytomegalovirus, herpes simplex (TORCH) serology and parvovirus serology did not show any sign of infection.

Anti-endomysium IgA and tissue transglutaminase IgA were negative in search of celiac disease. Stool microscopy was normal but steatocrit was ++ and +++ on two occasions. Sweat chloride test was elevated on two occasions, but no point mutations in cystic fibrosis gene were detected. Endoscopic biopsy of the duodenum revealed mild inflammation. Abdominal ultrasonography was normal.

Alpha-1 antitrypsin levels were within normal range, metabolic screening with tandem mass spectrometry, plasma, and urine amino acids were normal, and urine organic acids showed mild increase in ethyl malonic acid, adipic acid, and 3-OH sebamic acid. Cranial magnetic resonance imaging (MRI), which was performed for hypotonicity, showed symmetrical intensity changes on posterior pons, bilateral dentate nucleus, and basal ganglia, suspecting mitochondrial disease (►Fig. 1). Nevertheless, serum lactate and pyruvate levels and diffusion MRI were normal and MR spectroscopy did not show any lactate peak.

Serum levels of vitamin A, E, and D were normal, while serum amylase level was 15 U/L (N: 25–125), and lipase level was < 5 U/L (25–125). We started pancreatic enzyme and vitamin replacement with the diagnosis of pancreatic insufficiency.

One month later, her stool frequency decreased, hypotonicity was frankly improved, and she started to sit alone. However, her neutropenia persisted with neutrophil count of $0.45 \times 10^9/L$. Serum levels of iron, folic acid, and vitamin B12 levels were normal. During the following 10 days, her neutrophil count fluctuated as $0.45 \times 10^9/L$, $0.27 \times 10^9/L$, $1.52 \times 10^9/L$, $1.05 \times 10^9/L$, and $1.41 \times 10^9/L$. The bone marrow aspiration performed when her neutrophil count was $0.27 \times 10^9/L$, 8 days after admission, revealed moderate

cellularity and arrest in neutrophil differentiation at the myelocyte stage with mild dysplastic features in erythroid, monocytic, and neutrophilic series. No malign cell or any other abnormality was noted. The cytogenetic examination of bone marrow revealed 46,XX. Antinuclear antibody and anti-ds-DNA were negative. Complement 3 and 4 were normal, and Ig levels were normal for age except mild reduction in IgM (0.26, N: 0.3–1 g/L). Lymphocyte subsets were normal.

Abdominal MRI detected diffuse fatty infiltration of pancreas (pancreatic lipomatosis) (►Fig. 2). X-ray of thorax, head, and long bones revealed dysplasia of the left hip, acetabular subluxation, and widening of proximal and distal femoral metaphysis (►Fig. 3).

Genetic analysis of the SBDS gene revealed compound heterozygosity for NM-016038.3: c.183_184delinsCT (p.

Fig. 2 Abdominal MRI. Diffuse fatty infiltration of pancreas (pancreatic lipomatosis). MRI, magnetic resonance imaging.

Fig. 1 Cranial MRI. Symmetrical intensity changes on posterior pons (A), and globus pallidus (B), suspecting mitochondrial disease. MRI, magnetic resonance imaging.

Fig. 3 X-ray graphics. Dysplasia of the left hip, acetabular subluxation, and widening of proximal and distal femoral metaphyses.

K62*) (p.Lys62*)/c.258 + 2T > C (IVS2 + 2T > C), the two most common mutations responsible for SDS, thus confirming the diagnosis of SDS. The mutant genes in our patient were in transconfiguration, and the mother was a heterozygous carrier of NM-016038.3: c.258 + 2T > C (IVS2 + 2T > C), while the father was a heterozygous carrier of NM-016038.3: c.183_184delinsCT (p.K62*) (p.Lys62*) gene.

The family was informed about supportive measures for neutropenia and neutropenic diet and also neutropenic fever. She was prescribed granulocyte colony stimulating factor (G-CSF, 3–5 ug/kg subcutaneously) to be administered during infections. However, since she developed no infection during the 4 months of follow-up, she did not require G-CSF. The family members were started to be searched for human leukocyte antigen (HLA) compatibility.

Discussion

SDS is a rare autosomal recessive disease with a frequency of 1:77,000 to 1:100,000.^{1,2} Ninety percent of patients have mutations in the SBDS gene that is located on chromosome 7q11.³ The most common genetic mutations are c.258 + 2T > C and c.183–184TA > CT.^{1,3,4} To date, there is no observed genotype–phenotype correlation.^{1,4} Thirty-seven patients reported in the North American Registry for SDS, and 25 (67%) of them showed a compound heterozygous mutation of c.258 + 2T > C and c.183–184TA > CT.⁵ Similarly, our patient showed the NM-016038.3: c.183_184delinsCT (p.K62*) (p.Lys62*)/c.258 + 2T > C (IVS2 + 2T > C) mutation in compound heterozygous state.

SBDS gene encodes a protein that is involved in ribosomal maturation, microtubule stabilization, and actin polymerization, and plays a role in cell proliferation, mitosis, and stromal microenvironment of the bone marrow.³ p.K62* mutation, which was detected in our patient, in the SBDS gene is a truncating mutation. SBDS protein has 328 amino acids while this truncated protein just has 62. Mutation taster predicts this variant as a disease-causing mutation. According to the American Society of Human Genetics (ASHG) criteria, this is a null variant. The c.258 + 2T > C mutation is a splice site mutation and as it is in the +2 position in intron 2, according to the ASHG criteria, this is also a null variant. The Human Splicing Finder software predicts this variant as a splicing defect-causing variant. This variant was given as a pathogenic variant in the ClinVar database by several submitters.

It is also important to note that absence of a SBDS gene mutation does not rule out the diagnosis of SDS.³ Although 90% of the patients with classical presentation have mutations in the SBDS gene, the rest of the patients with a clinical diagnosis of SDS may not establish known mutations. Recently, DNAJ21 and EFL1 gene mutations were also reported to cause clinical features of SDS. These two genes also encode proteins involved in ribosome biogenesis pathway.^{6,7} Yet, it is still unclear if these mutations constitute different types of ribosomopathies with overlapping features.

There are only two genetically confirmed SDS cases reported from Turkey and both patients had the similar compound heterozygous mutation.^{2,8} Compound heterozygous mutations also seem to be leading SDS mutations in our country.

Exocrine pancreatic failure in SDS usually presents within the first year of life and is due to depletion of pancreatic acinar cells and fatty infiltration.¹ Low levels of pancreatic isoamylase or cationic trypsinogen may be used for diagnosis, but these enzyme levels vary with age. Low levels of pancreatic elastase, reduced levels of fat soluble vitamins, or increased fecal fat can be more useful to detect pancreatic failure.^{1,9,10} Pancreatic MRI may reveal pancreatic lipomatosis but normal radiologic studies do not rule out SDS, as these changes may emerge later in time.⁵ Although levels of fat-soluble vitamins were normal in our patient, excretion of stool fat was increased, and lipase level was below the normal age range and MRI showed a fatty pancreas. Putting all of the findings into consideration may help a better evaluation of pancreatic sufficiency especially in small children.

Nonspecific duodenal inflammation findings in endoscopic duodenal biopsies of half of the patients with SDS may suggest a possible enteropathic component.¹¹ Correspondingly, our patient had mild duodenal inflammation. Whether this finding is a part of SDS or related with malabsorption is a question of interest, control duodenal biopsies after correction of malabsorption may give a better explanation.

Elevated liver transaminases and hepatomegaly can be observed in SDS, but tend to resolve by age 5 years.^{1,12} Our patient had mild hepatomegaly and increase in aspartate transaminase-alanine transaminase (AST-ALT) levels. Although

these findings tend to resolve by time, they may cause difficulty in differential diagnosis.

Hematologic abnormalities in SDS include hypoproliferative cytopenias, varying degrees of hypocellularity/fatty infiltration of the bone marrow, and increased risk of myelodysplasia and acute myeloid leukemia.¹ Persistent (one-third of cases) or intermittent (two-thirds of cases) neutropenia (absolute neutrophil count $< 1 \times 10^9/L$ in 2 weeks to 12 months of age, $< 1.5 \times 10^9/L$ over 12 months of age) is an absolute finding in almost all of the patients. Although neutropenia usually presents before the diagnosis of the disease, it may develop over time.¹³ Similarly, our patient had neutropenia at the time of admission that fluctuated during the follow-up that could not be attributed to other causes. Neutropenia may be an important clue for the diagnosis especially when other distinctive features of the disease have not been revealed yet. Anemia (in 46%), thrombocytopenia (in 42%), and pancytopenia (in 21%) are also encountered in SDS.¹⁴ In our patient, during the 4 months of follow-up, no anemia and thrombocytopenia developed.

Skeletal abnormalities are present in almost every patient with SDS but vary among individuals and may be detected later in life.^{1,2,4,15} The most common deformity is abnormal development of metaphyseal growth plates (metaphyseal chondrodysplasia).⁵ Thickening and irregularity of growth plates usually occur in the first 2 years of life and tends to worsen with age.⁵ These changes can be subtle in the first months of life, as our patient's bone survey reported left acetabular subluxation, widening of metaphysis of the left hip, and bilateral proximal and distal femur.

Aggett et al, in 1980, analyzed 21 clinically diagnosed SDS cases in detail and noted that hypotonia was frequent particularly in infancy, and secondary to feeding and infectious problems.¹⁶ They also included that profound hypotonia might suggest a defect primary to the syndrome itself.¹⁶ Topa et al reported myopathic changes in muscle biopsy of an infant with SDS who presented with neonatal thoracic dystrophy and severe hypotonia.¹⁷ We did not perform a muscle biopsy in our patient; however, she had a less severe and transient hypotonia that improved with nutritional support. So, her hypotonia was less likely to be related with myopathic changes.

Structural brain changes as well as cognitive and behavioral impairment can be seen in patients with SDS.¹ Brain MRI images of patients with SDS showed smaller posterior fossa and cerebellar vermis, corpus callosum, and brainstem than healthy controls which may be related to neuropsychological features.¹⁸ Another study reported diffuse changes in gray and white matter of patients with SDS that leads to cognitive impairment.¹⁹ Our patient had developmental and motor delay. Her MRI revealed symmetrical intensity changes on the posterior pons, bilateral dentate nucleus, and basal ganglia.

Our patient is a unique SDS case, as she applied with features of neurometabolic disease. Her developmental defect may be related with a delay in myelination due to severe malnutrition, since her motor functions improved with treatment, but also MRI changes may be related with

neurological findings of SDS. Serial MRI is needed for a better explanation.

In conclusion, SDS is a multisystemic disease with various clinical findings. It should be included in differential diagnosis of patients with failure to thrive and unexplained neurodevelopmental delay with neutropenia.

Conflict of Interest

There is no conflict of interest related directly or indirectly to the subject of this article. None of the authors have any financial interests or affiliations with institutions, organizations, or companies that are mentioned in the manuscript or whose products or services are discussed. All of the authors contributed equally in designing, drafting, and revising the work.

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