Shwachman–Diamond syndrome mimicking mitochondrial hepatopathy

Odelya Kaufman[1] | Colleen Donnelly[1] | Emalyn Cork[1] | Maria I. Fiel[2] | Jaime Chu[3] | Jaya Ganesh[1]

[1]Department of Genetics and Genomics, Mount Sinai Hospital, New York, New York, USA

[2]Department of Pathology, Mount Sinai Hospital, New York, New York, USA

[3]Division of Pediatric Hepatology at Kravis Children's Hospital, Mount Sinai Hospital, New York, New York, USA

Correspondence
Jaya Ganesh, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, One Gustave L Levy Pl, Box 1497, New York, NY 10029, USA.
Email: Jaya.ganesh@mssm.edu

Abstract

Shwachman–Diamond syndrome (SDS) is a genetic disorder caused by mutations in the Shwachman–Bodian–Diamond syndrome (SBDS) gene. The syndrome is characterized by multiorgan dysfunction primarily involving the bone marrow and exocrine pancreas. Frequently overlooked is the hepatic dysfunction seen in early childhood which tends to improve by adulthood. Here, we report a child who initially presented with failure to thrive and elevated transaminases, and was ultimately diagnosed with SDS. A liver biopsy electron micrograph revealed hepatocytes crowded with numerous small mitochondria, resembling the hepatic architecture from patients with inborn errors of metabolism, including mitochondrial diseases. To our knowledge, this is the first report of the mitochondrial phenotype in an SDS patient. These findings are compelling given the recent cellular and molecular research studies which have identified SBDS as an essential regulator of mitochondrial function and have also implicated SBDS in the maintenance of mitochondrial DNA.

KEYWORDS

elevated transaminases, failure to thrive, SDS

1 | INTRODUCTION

Shwachman–Diamond syndrome (SDS) is a rare genetic syndrome characterized by multiorgan dysfunction primarily involving the bone marrow and exocrine pancreas. Common features of SDS include cytopenias due to bone marrow hypoplasia, exocrine pancreatic insufficiency, and failure to thrive (FTT) during infancy. Less commonly, SDS can also present with elevations in hepatic transaminase levels and/or hepatomegaly. SDS is an autosomal recessive genetic disorder caused primarily by mutations in the Shwachman–Bodian–Diamond syndrome (SBDS) gene, which is thought to be required for ribosome function and protein translation.

2 | CASE PRESENTATION

The patient was born at term after an uncomplicated pregnancy. Her birthweight and length were normal, however at 5 months of age she was noted to have poor weight gain and poor linear growth, and truncal hypotonia. Due to concerns for FTT, the patient had subspecialty evaluations with pediatric cardiology, endocrinology, and pulmonology that were normal. At 6 months of age, she had a gastrointestinal evaluation that revealed mildly elevated transaminases (AST 190 U/L [normal < 35]; ALT 198 U/L [normal < 45]). Her fecal qualitative fat, celiac-associated immunoglobulins, bilirubin, GGT, albumin, and INR were within normal limits. She had genetics evaluations with

nondiagnostic microarray, mitochondrial gene panel, and whole exome sequencing.

At presentation at 11 months of age, she weighed 6.7 kg (<1%ile, WHO Girls), and her length was 67 cm (4%ile, WHO Girls). She was alert and interactive with age-appropriate fine motor, language, and social skills, however, she had a persistent gross motor delay. On physical examination, she appeared small for age with mild facial dysmorphism that included a broad forehead with frontal upsweep of hair, epicanthic folds, and stellate irises (Figure 1A). Notably, she had a small bell-shaped thorax (Figure 1B). Cardiac, lung, and abdominal exams were normal.

Due to persistent elevation of transaminases, the patient had a liver biopsy at 13 months of age. On microscopic examination with hematoxylin and eosin stain (H&E), the hepatic architecture showed mild portal septal fibrosis, and lobules with scattered small and large droplet steatosis (Figure 2A). Electron microscopy (EM) revealed relatively normal histoarchitecture with the notable exception of hepatocytes filled with numerous small mitochondria and abundant lipid droplets of variable sizes. The smooth and rough endoplasmic reticulum, Golgi complexes, and peroxisomes had normal appearance, and there was normal intracellular content of glycogen (Figure 2B). The findings were thought to be consistent with a metabolic disorder, however screening tests for metabolic conditions including acylcarnitine profile, plasma amino acids, urine organic acids, and carbohydrate deficient transferrin were normal.

Given the nonspecific liver biopsy findings, work up was broadened to include whole genome sequencing which revealed compound heterozygous pathogenic variants in the SBDS gene (maternal c.183_184del-TAinsCT, p.K62*; paternal c.258+2 T > C, p.?) consistent with SDS. Following molecular diagnosis, the parents noted the onset of pale-colored stools with increased stool frequency. Pancreatic insufficiency was confirmed with reduced pancreatic elastase (not previously assessed), though fecal fat remained normal. She was started on pancreatic enzyme replacement with immediate improvement in stool consistency and weight gain. The patient was also referred to hematology for further management and surveillance of cytopenia.

3 | DISCUSSION

SDS is a rare genetic syndrome characterized by multiorgan dysfunction with typical presenting features that include exocrine pancreatic, hematologic, and skeletal abnormalities. Hepatic involvement is present in up to 40% of patients.[1] A retrospective review of 12 SDS patients found that children under 3 years of age consistently demonstrated elevations in transaminase levels.[2] Fortunately, SDS-related liver disease has an overall good prognosis, as the elevates transaminases, hepatosteatosis, and fibrosis tend to normalize around 5 years of age. Adult patients with SDS usually have no evidence of clinical liver disease, with few rare exceptions.[2,3]
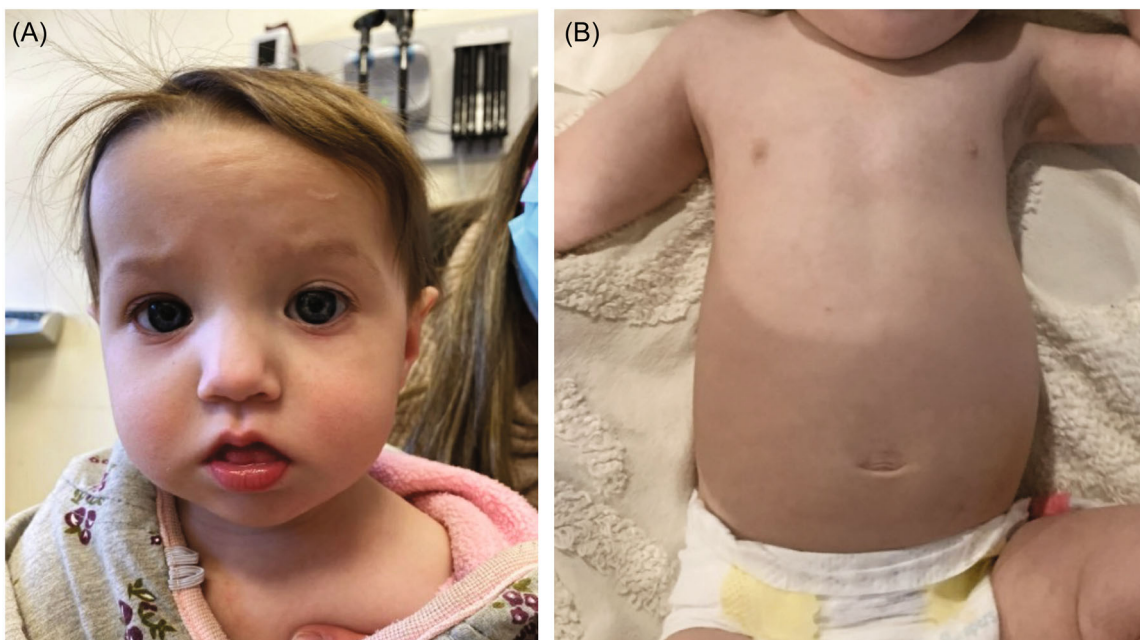

FIGURE 1 Patient's physical features. (A) Photograph featuring minor facial dysmorphisms: broad forehead with frontal upsweep of hair, epicanthic folds, and stellate irises. (B) Photograph featuring bell-shaped thorax.
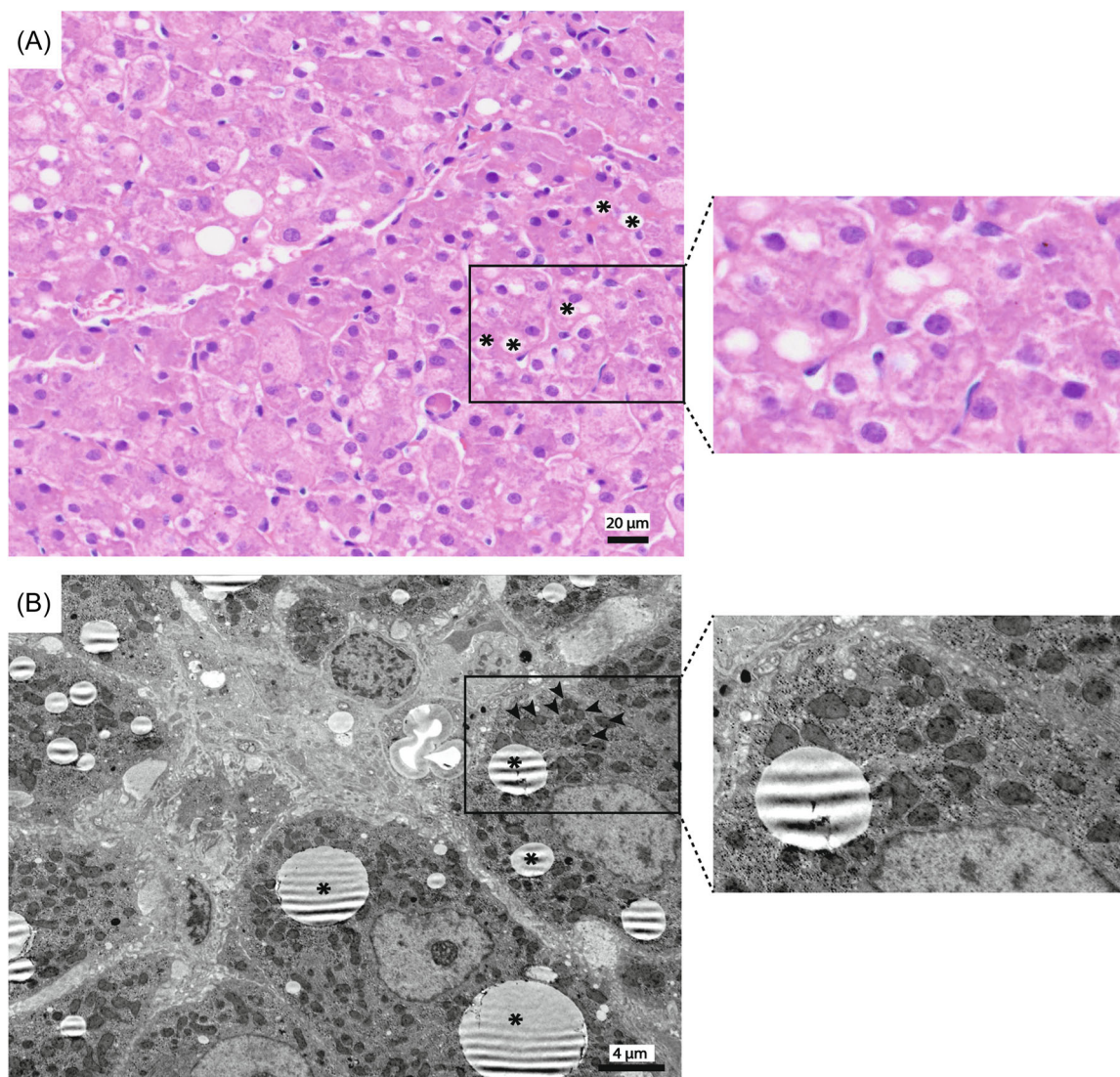
FIGURE 2 Pathology specimens from pediatric Shwachman–Diamond syndrome liver biopsy. (A) Representative hematoxylin and eosin stained high-magnitude magnification (×40) of liver biopsy demonstrating lipid droplets (asterisks); inset magnified for clarity. (B) Representative electron microscopy demonstrating intrahepatic lipid droplets (asterisks) and numerous small mitochondria (arrowheads); inset magnified for clarity.

The hepatic pathology of patients with SDS has not been well characterized. To our knowledge, there have been three descriptions of SDS liver biopsy results which described periportal fibrosis, microsteatosis, and inflammation.[2,4] The prior reports of cellular-level hepatic pathology are similar to that seen for the patient described herein. However, ultrastructural analysis of SDS-related hepatic pathology has not been previously reported. In our patient, EM on liver biopsy specimens was notable for numerous small mitochondria that were densely packed within the cytoplasm, reminiscent of "oncocytic transformation" usually seen with the primary mitochondrial condition, mitochondrial DNA depletion syndrome.[5,6] Mitochondrial DNA depletion syndrome is caused by particular mutations in mitochondrial genes that cause quantitative reduction of mitochondrial DNA and dysfunctional oxidative phosphorylation; notably this syndrome is also associated with hepatic dysfunction.[5,6] Another relatively common pediatric mitochondrial disorder, Pearson Syndrome, is caused by large contiguous deletions of mitochondrial DNA. The cellular phenotype for Pearson Syndrome is more often associated with large mitochondria (i.e., megamitochondria) that have reduced and abnormal cristae morphology.[7] Despite this difference in mitochondrial morphology, it is fascinating that the primary clinical features of both SDS and Pearson syndrome are marrow suppression and pancreatitis.

The SBDS protein is thought to play various roles in essential cellular pathways including ribosomal biogenesis,[8–10] mitotic spindle stabilization,[11,12] actin

TABLE 1 Comparison of human phenotype ontology (HPO) terms with phenotypes utilized during analysis of initial whole exome sequencing (WES) and whole genome sequencing (WGS).

Relevant OMIM phenotypes	WES HPO terms utilized	WGS HPO terms utilized
Developmental delay	Gross motor delay	Gross motor delay
Failure to thrive	Failure to thrive	Failure to thrive
Abnormal liver function tests	Elevated liver enzymes	Elevated liver enzymes
Narrow thorax		Small thoracic cage
Smaller OFC (relative microcephaly)		Mild microcephaly
Nonoverlapping terms		
	Elevated thyroglobulin levels	Generalized hypotonia Hepatic fibrosis Hepatic steatosis Hypertelorism Epicanthal folds Bulbous nose

Note: The HPO terms associated with genetic disorders on the curated database Online Mendelian Inheritance of Man (OMIM) are generally considered to be the clinical standard. For complete list of OMIM phenotypes associated with SDS, visit https://omim.org/clinicalSynopsis/260400.
Abbreviation: OFC, orbital frontal cortex.

polymerization,[13] and mitochondrial function.[13–15] The link between SBDS protein function and mitochondrial health was first described in 2013 when yeast biologists noted that cells lacking the yeast ortholog of SBDS (SD01) had impaired respiratory function as measured by increased production of reactive oxygen species.[14] The study authors also demonstrated similar deficits in respiratory function in human cells depleted of SBDS.[14] Interestingly, further yeast studies found that lack of functional SD01 resulted in depletion of mitochondrial DNA (mtDNA), with the authors hypothesizing that the maintenance of mtDNA was compromised due to oxidative damage.[15] Human lymphoblast cells from SDS patients were also found to have decreased Complex IV activity and thereby decreased ATP production.[16]

It is noteworthy that the patient's initial genetic testing, including WES, did not uncover the diagnosis of SDS. While WES can detect most pathogenic variants, it is limited to those variants found in coding regions (exons) as well as splice-site mutations. On the other hand, WGS can additionally detect intronic and other noncoding variants, as well as copy number variants and tri-nucleotide expansions, and has an increased diagnostic rate of about 20%.[17] Interestingly, the SBDS gene variants that were ultimately identified on the patients WGS were within genetic regions that could have been identified on WES, with one variant within exon 2 (c.183_184delTAinsCT), and the other a 5′ donor splice-site mutation between exons 2 and 3 (c.258 + 2T >

C). This is significant because c.183_184delTAinsCT and c.258 + 2T > C are two of the most common pathogenic variants in SBDS.[18] Another consideration for WES and WGS are the human phenotype ontology (HPO) terms that are input to the analytical pipeline. In this case, the WGS testing included two additional terms that may have provided the necessary clinical information for the diagnosis (Table 1). While the clinical laboratory declined to clarify the technical or analytic reasons for the missed diagnosis, there is a known complication of misalignment between sequence reads of the SBDS gene and its pseudogene, SBDSP1 due to sequence homology which can potentially raise the threshold of detection.[19]

4 | CONCLUSION

Here, we report a child with SDS that initially appeared to have clinical features of a mitochondrial disorder including FTT and elevated transaminases, and a liver biopsy with ultrastructural features resembling mtDNA depletion syndrome. To our knowledge, this is the first report of the cellular mitochondrial phenotype in an SDS patient, with numerous small mitochondria found on hepatic biopsy. Given these findings, it is fascinating that recent cellular and molecular studies have identified SBDS as an essential regulator of mitochondrial health, and in the maintenance of mtDNA. Perhaps it is not coincidental that SDS and primary mitochondrial disorders affecting pediatric patients share significant clinical overlap, as these disease processes may share impaired mitochondrial respiration as an underlying pathology.

CONFLICT OF INTEREST STATEMENT
The authors declare no conflict of interest.

ETHICS STATEMENT
Informed consent for publication of the article and use of patient photographs was obtained from the patient's parents.

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