Diagnosis, Treatment, and Molecular Pathology of Shwachman-Diamond Syndrome

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KEYWORDS

• Shwachman-Diamond syndrome • Bone marrow failure • Ribosome
• Pancreatic dysfunction • Neutropenia • Failure to thrive

KEY POINTS

- SDS is a challenging marrow failure disorder with exocrine pancreatic dysfunction and diverse clinical phenotype.
- Ongoing advances in ribosomal biogenesis and cellular function contribute to defining the pathogenesis of the molecular phenotype of SDS, with novel candidate genes recently described.
- Further natural history and collaborative efforts are essential to define disease manifestations, prevent known complications, and ensure new and targeted therapies to ameliorate and prevent malignant transformation.

INTRODUCTION

Shwachman-Diamond syndrome (SDS) is an autosomal-recessive inherited bone marrow failure (BMF) disorder characterized by exocrine pancreatic dysfunction, BMF, and predisposition toward myelodysplasia syndrome (MDS) or acute leukemia, particularly acute myeloid leukemia (AML). SDS is rare, with an estimated incidence of 1/76,000.[1] Many different body systems are affected, including the skeletal, cardiac, endocrine, nervous, hepatic, and immune systems, although these are not universally affected in all patients, or even within family cohorts.

SDS is a disorder of ribosomal biogenesis, with approximately 90% of individuals having biallelic mutations in the Shwachman-Bodian-Diamond Syndrome (SBDS) gene located on chromosome 7q11. Although the role of the SBDS protein is yet to be fully established, it is thought to play an integral part in ribosomal maturation,

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and cellular proliferation and the hematopoietic microenvironment. Recently three additional genes associated with ribosome assembly or protein translation (DNAJC21, ELF1, and SRP54) were reported in association with an SDS phenotype.[2–4]

There is great phenotypic diversity among individuals with SDS, despite most sharing one or more common allelic mutations within *SBDS*. Given its rarity, the understanding of the pathogenesis, phenotype, treatment, and outcomes has been limited to case series and reports from new registry studies. Similarly, guidelines on management and treatment are based primarily on expert consensus and small cohort studies. Ongoing large collaborative studies are needed to further define the pathogenesis, treatment, and natural history of SDS to improve clinical practice and promote investigation in novel therapeutic approaches.

This article focuses on the diagnosis, treatment, and molecular pathology of SDS and recent insights into this disease.

CLINICAL MANIFESTATIONS

Bone marrow and pancreatic dysfunction as described in the most recent consensus guidelines (**Box 1**) are the classic clinical features of SDS. In the North American SDS registry, however, only 51% (19 of 37) of those with biallelic *SBDS* mutations presented with classic findings of neutropenia with steatorrhea.[5] In fact, 14% had no

Box 1
Clinical and molecular diagnostic features of Shwachman-Diamond syndrome

Diagnostic Criteria

Biallelic SBDS mutations known or predicted to be pathogenic, or mutations in other SDS-associated genes DNAJC21, ELF1, SRP54 (autosomal dominant)

Clinical Diagnosis

Hematologic features (present on at least two occasions)

- Neutropenia (absolute neutrophil count <1500)
- Anemia or macrocytosis (unexplained by other causes, such as iron/B_{12} deficiency)
- Thrombocytopenia (platelet count <150,000) on at least two occasions
- Bone marrow findings
  - Hypocellularity for age
  - Myelodysplasia
  - Leukemia
  - Cytogenetic abnormalities

Pancreatic features

- Reduced levels of pancreatic enzyme relevant to age
  - Trypsinogen <3 years
  - Isoamylase >3 years
- Low levels of fecal elastase
- Supportive features
  - Abnormal pancreatic imaging with lipomatosis
  - Elevated fecal fat excretion >72 hours

Additional supportive features

- Skeletal abnormalities including thoracic dystrophy
- Neurocognitive/behavioral problems
- Unexplained height less than third percentile
- First-degree family member with SDS

Adapted from Dror Y, Donadieu J, Koglmeier J, et al. Draft consensus guidelines for diagnosis and treatment of Shwachman-Diamond syndrome. Ann N Y Acad Sci 2011;1242(1):43; with permission.