

## GRAND ROUNDS

# Shwachman-Diamond syndrome: Report from an international conference

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This report was first conceived during the International Shwachman-Diamond syndrome (SDS) Family Conferences, and further developed by Medical and Scientific participants attending the First International Scientific meeting on SDS. Through a combination of literature review and consultations with specialists with clinical expertise in the management of patients with SDS, we sought to answer several questions regarding SDS. This report is directed to physicians and health care workers interacting with affected individuals and their families. Each is faced with the challenging task of establishing the diagnosis, promoting adequate follow-up, and preventing complications.

## WHAT IS KNOWN ABOUT SHWACHMAN-DIAMOND SYNDROME?

In 1964, Shwachman, Diamond, Oski, and Khaw from the United States<sup>1</sup> and Bodian, Sheldon, and

Lightwood from Great Britain,<sup>2</sup> reported a series of young patients with failure to thrive in infancy and exocrine pancreatic insufficiency with diarrhea and hematologic abnormalities, especially neutropenia but also varying degrees of anemia and thrombocytopenia. Biopsy specimens of the pancreas in selected patients revealed adipose tissue replacement of the acini with preserva-

See editorial, p 164,  
and related article, p 259.

tion of the Islets of Langerhans. The bone marrow was hypoplastic with increased fibrosis and fat; many patients had hepatomegaly, and one patient in each group had fatty infiltration and early fibrosis on liver biopsy. Three years later, Burke et al<sup>3</sup> detailed a series of 19 patients with SDS in Australia. Approximately half the patients had malabsorption and steatorrhea related to pancreatic dysfunction, and the other half were evaluated for neutropenia; they also stressed the risk of life-threatening infection. Aggett et al<sup>4</sup> reiterated

the previously described features of SDS and added emphasis to the chondrodysplastic skeletal anomalies, including metaphyseal dysostosis and rib abnormalities. Although metaphyseal changes are generalized in other chondrodysplastic disorders, the changes are more localized in SDS, and the hips and knees appear to be more severely affected. The propensity for patients with SDS to have acute myelogenous leukemia (AML) raises a new concern for the long-term course.<sup>5</sup> A detailed analysis of a large cohort of affected individuals and families strengthened the notion that SDS is a single entity by demonstrating the similarities in the phenotypic manifestations between sibling sets and isolated cases.<sup>6</sup> Nevertheless, considerable heterogeneity of the exocrine pancreatic and hematologic phenotypes was noted.<sup>6,7</sup> Among affected sibling sets, there was little concordance for the hematologic abnormalities but a high degree of concordance for the exocrine pancreatic dysfunction.<sup>6</sup>

AML Acute myelogenous leukemia  
G-CSF Granulocyte colony stimulating factor  
SDS Shwachman-Diamond syndrome

The Table identifies the major clinical phenotypes of SDS. It appears that in patients with SDS, the ductal function of the pancreas (production of water and electrolytes) is preserved, but the exocrine enzyme secretion is severely curtailed,<sup>7,8</sup> at times leading to steatorrhea. Histology of the pancreas shows preserved ducts and paucity of acini

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with fatty replacement; yet, with time, the pancreatic enzyme release and the fat absorption not only stabilize but may gradually normalize in a fair number of patients.<sup>8</sup> This is why the diagnosis of SDS may be difficult in an older child, who may have normal fat balance studies. However, improved exocrine pancreatic insufficiency does not necessarily imply improved growth, because short stature is a frequent clinical feature of SDS caused by skeletal abnormalities. Similarly, the elevated aminotransferase levels seen in early childhood often regresses with age.<sup>7</sup> Bone marrow dysfunction can show similar variability. Some individuals with SDS show persistent neutropenia; others show cyclic or intermittent variation in their counts even affecting other cell lines or causing pancytopenia.<sup>6,9</sup> During an acute illness, the absolute neutrophil count may be normal.

The referenced series also describe a large array of less common clinical problems in individuals with SDS, some of which may be part of the syndrome. These disorders include cleft palate, ichthyosis, dental abnormalities, dysmorphic facial features, functional and anatomic urinary tract abnormalities, Hirschsprung disease,<sup>3-8</sup> and nephrocalcinosis and myocardial fibrosis.<sup>10,11</sup>

## HOW IS THE DIAGNOSIS OF SDS ESTABLISHED?

SDS is an autosomal recessive clinical syndrome of unknown cause,<sup>12</sup> for which there is no specific pathognomonic test. SDS emerges as a clinical phenotype with the central features of pancreatic exocrine and bone marrow dysfunction; these two features are essential for the diagnosis albeit variable between SDS individuals and even within the same individual over time. Other syndromes producing pancreatic exocrine dysfunction must be excluded

**Table.** Spectrum of clinical problems in SDS

Organ	Manifestation	Key references
Exocrine pancreas	Steatorrhea <sup>*</sup>	3, 4, 7, 8
	Impaired enzyme output <sup>*</sup>	7-9
	Low serum trypsinogen <sup>*</sup>	6-8
	Abnormal imaging	14
Blood counts	Neutropenia	1, 3, 6, 9
	Intermittent	3, 4, 6
	Persistent	5, 9
	Anemia	1, 3-7, 9
	Thrombocytopenia	1, 3-7, 9
Bone marrow	Hypocellular marrow,	6, 17, 18
	Aplastic anemia	
	Myelodysplasia	5, 6
	AML	5, 7, 15, 16
	ALL	9
	Abnormal cytogenetics	16, 19, 20
Liver	Elevated transaminases <sup>*</sup>	6, 9, 30, 31
	Steatosis, fibrosis	7
Heart	Myocardial fibrosis	10
Skeletal problems	Rib cage abnormalities	4, 6, 9
	Short ribs/flared ends	4, 32
	Metaphyseal dysostosis	2, 4, 7, 32
Growth	Short stature	4, 6, 7
	Pubertal delay	4
Infections	Respiratory	3, 4, 6, 7
	Systemic	4, 6, 7
Developmental problems	Delayed development	4, 9, 33
	Low IQ	4, 9
	Learning disorders	33

<sup>\*</sup>May normalize later.

during the initial diagnostic evaluation. Cystic fibrosis, Pearson's syndrome, Johanson-Blizzard syndrome, and severe malnutrition present with diminished exocrine pancreatic function. Other bone marrow failure syndromes warrant consideration, particularly if hematologic manifestations provide the first clinical evidence of SDS.<sup>13</sup> Pearson's syndrome, Fanconi anemia, and Diamond-Blackfan anemia can be excluded by clinical or bone marrow findings or by specific laboratory tests. Transient neutropenia can occur in relation to medications and infections. Infants can show benign neutropenia without clinical sequelae or underlying disease. Repeated demonstration of significant decrements in blood counts is

essential to an accurate SDS diagnosis. Variations in disease severity and clinical manifestations complicate the establishment of a definitive diagnosis.

### *Exocrine Pancreas*

To establish pancreatic acinar dysfunction, one or more of the following conditions must be documented: (1) pancreatic stimulation testing with intravenous pancreozymin with/without secretin: direct quantitative measurement of pancreatic enzymes demonstrates low values<sup>7-9</sup>; (2) documentation of low concentration of serum immunoreactive trypsinogen (normal values do not exclude the diagnosis, especially after age 3 years)<sup>6,7</sup>; and (3) abnormal fecal fat balance study (72-

hour collection) with no evidence of intestinal mucosal disease or cholestatic liver disease<sup>1,3-5,8</sup> and a pancreatic imaging study demonstrating a small or fatty pancreas.<sup>8,14</sup>

### ***Bone Marrow***

To establish bone marrow dysfunction, one or more of the following must be demonstrated: (1) neutropenia with an absolute neutrophil count <1500 neutrophils/mm<sup>3</sup>.<sup>1,3-7,9</sup> Neutropenia can be persistent, cyclic, or intermittent but must be documented at multiple time points (at least 3 times over ≥3 months); (2) anemia with a hemoglobin concentration below the age-related normal range. Macrocytosis for age is often evident.<sup>1,3-7,9</sup>; (3) thrombocytopenia with a platelet count <150,000 platelets/mm<sup>3</sup>.<sup>1,3-7,9</sup>; (4) pancytopenia<sup>7</sup>; and (5) myelodysplastic syndrome documented on bone marrow examination.<sup>5,6,13</sup>

### ***Supportive Features***

The most frequent supportive features of SDS include skeletal abnormalities, hepatomegaly, elevation of serum aminotransferase levels, short stature, and frequent infections, particularly of the respiratory system. These features may support the diagnosis of SDS, but their absence does not exclude the diagnosis.

## **HOW SHOULD PERSONS WITH SDS BE ASSESSED AT DIAGNOSIS AND OVER TIME?**

### ***At Diagnosis***

After a complete history and a thorough physical examination, including growth parameters and nutritional status, we recommend a complete blood count with differential count and platelet level, serum aminotransferase levels, skeletal survey, vitamins A, D (25-OH vitamin D), and E levels, prothrombin time and partial thromboplas-

tin time, 72-hour fecal fat collection, bone marrow aspirate, biopsy, and cytogenetic studies. After the diagnosis of SDS is established, initial follow-up visits should occur every 1 to 3 months to ascertain efficacy of instituted treatments, to help the patient and family adjust to the diagnosis, and to provide educational review. Primary care providers (pediatricians, general practitioners, nurse practitioners) supply anticipatory guidance, education, and support to help patients and their families face a long-term chronic disorder with an uncertain course.

### ***Reassessment Every 6 to 12 Months***

Assessment should include (1) weight, length or height, assessment of pubertal development, review of developmental progress, and evaluation of nutritional status; (2) complete blood count with white cell differential and platelet count (or more often as clinically indicated); and (3) serum concentrations of vitamin A, vitamin E, 25-OH-vitamin D, and prothrombin time/partial thromboplastin time.

Annual evaluation by a pediatric gastroenterologist and a pediatric hematologist can be an aid to effective and comprehensive clinical care, a source of information for patients and families, and a gateway to potential studies of this disorder. For specific problems, for example, metaphyseal dysostosis, dental disorders, or learning difficulties, additional specialized consultation may be required. Recommended follow-up evaluations can be performed by the primary care giver or by the subspecialist.

### ***Reevaluation Every 1 to 2 Years of the Necessity of Continuing Pancreatic Enzyme Supplementation***

Steatorrhea may resolve with increasing age, even though pancreatic enzyme secretion may not reach normal levels<sup>6,9</sup>; this usually occurs within the first 4 years of life. Thus, periodic reassessment of steatorrhea and the

need for supplemental pancreatic enzymes is recommended. Analysis of fat absorption with a 72-hour fecal fat collection after the individual has discontinued enzyme supplementation for at least 48 hours is the optimal method for reassessment, although serial trypsinogen levels might also provide adequate information.<sup>7</sup>

### ***Review Serial Hematologic Parameters***

Patients should be referred to a hematologist as soon as SDS is diagnosed. It is recommended, based on the experience of the authors in other bone marrow failure syndromes, that bone marrow aspirates, biopsies, and cytogenetic studies should be done at diagnosis, then annually or more often if needed for clinical evaluation. Currently, SDS is considered a bone marrow failure syndrome with potential for progression to aplastic anemia, myelodysplastic syndrome, or acute myelogenous leukemia.<sup>15-18</sup> The exact magnitude of risk is unclear because no longitudinal or serial examinations of bone marrow have been performed prospectively in patients with SDS. Bone marrow chromosomal abnormalities have been reported in several patients with SDS.<sup>16,19,20</sup> In other bone marrow failure syndromes, myelodysplasia and/or clonal chromosomal abnormalities may be harbingers of leukemia. In SDS, limited clinical experience suggests that such bone marrow findings can be transient and may not be progressive. Bone marrow aspirate or biopsy specimens should be reviewed in the context of peripheral cytopenias and the patient's clinical status. A high level of concern about bone marrow findings may lead to re-examination of bone marrow within 6 to 12 months or sooner. Serial bone marrow evaluation may elucidate progression of morphologic or clonal abnormalities.

Consideration should be given for long bone films and referral to an orthopedic surgeon if symptoms and

physical examination indicate skeletal abnormalities.

## TREATMENT CONSIDERATIONS

### *Severe Neutropenia*

Severe neutropenia (ANC <500 neutrophils/mm<sup>3</sup>) associated with repeated infections may lead to consideration of treatment with prophylactic antibiotics or granulocyte colony stimulating factor (G-CSF). Although long-term administration of G-CSF to patients with severe chronic neutropenia may play a role in the development of hematologic malignancies, this role has not been clearly defined,<sup>21</sup> and there is still insufficient evidence at this time to determine whether it will increase the already high risk of development of leukemia in these patients. Neutrophil chemotactic abnormalities are described in some patients with SDS.<sup>22,23</sup> No specific therapy has been suggested.

### *Malabsorption*

Malabsorption is treated with pancreatic enzymes as well as with supplemental fat-soluble vitamins. Reports describing patient cohorts indicate improved weight with this therapy.<sup>1,3-5,8</sup> Specific nutritional deficiencies may require appropriate supplements.

Some manifestations, particularly short stature, have no specific therapy. Growth velocity is often normal, but short stature persists<sup>7-9,12</sup> despite normal levels of growth hormone. Pubertal progress may be delayed.<sup>7</sup> Consultation with an orthopedic surgeon is recommended, especially for problems of the hips and knees.

Because of the known risk of development of AML, bone marrow transplantation has been performed in a small number of patients with SDS.<sup>24,25</sup>

Much of the long-term course of this disorder is unknown because longitudinal data have not been systematically collected for a large patient cohort.

## WHAT IMPORTANT ISSUES REQUIRE FURTHER DEFINITION IN SDS?

These issues include (1) delineation of the molecular basis of SDS; (2) development of a specific diagnostic test for SDS; (3) detailed longitudinal documentation of the clinical phenotype of SDS and its natural history, including (a) hematologic outcomes, including progression to aplastic anemia, myelodysplastic syndrome, and acute leukemia and their interrelation, if any; (b) the role of G-CSF in the evolution to a myelodysplastic syndrome or leukemia; (c) pancreatic dysfunction, including pertinent age-related developmental aspects of the different exocrine enzymes; (d) growth, development and learning disorders; and (e) skeletal complications and dental disorders.

To achieve these goals, research priorities should include (1) collecting longitudinal clinical data about the SDS phenotype, through an international cooperative effort; (2) identifying the genetic basis of SDS and characterizing the affected gene as well as the function and interactions of the gene product. The development of animal models could then also be possible; (3) defining the disease pathobiology in the various affected organs; and (4) investigating the bone marrow failure and all associated complications in order to identify markers of disease condition and progression, as well as provide improved strategies to treat marrow failure and prevent infections.

Studies have established that chromosome 7 markers at the centromeric region show linkage with the disease, providing a critical clue toward the identification of the affected gene.<sup>26</sup> To better understand the bone marrow dysfunction, Dror and Freedman<sup>19</sup> have investigated the relation between the marrow environment and hematopoietic progenitors to determine that

problems probably occur in both in SDS. They have also shown a tendency for SDS marrow mononuclear cells to show increased apoptosis.<sup>27</sup> These findings may be reflecting faulty proliferative properties of bone marrow cells that lead to the cytopenias. Finally, studies on bone marrow samples of patients with SDS suggest a possible role for granulocytic surface marker analysis and p53 overexpression on biopsies as potential tools to investigate disease progression.<sup>28,29</sup>

## CONCLUSIONS

As with many rare genetic disorders, proper identification of patients is paramount in planning therapy and follow-up strategies. Despite 40 years since its original description, SDS continues to pose challenging issues in its diagnosis, treatment, and in understanding its underlying genetic defect. This report is an attempt to bring together the available information regarding SDS to standardize patient diagnosis, treatment, and follow-up. In addition, this report attempts to highlight specific questions and major areas where knowledge is lagging in order to direct future research.

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