Variable Clinical Presentation of Shwachman–Diamond Syndrome: Update from the North American Shwachman–Diamond Syndrome Registry

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Objectives To investigate the range of clinical presentations for Shwachman–Diamond syndrome (SDS) with the long-term goal of improving diagnosis.

Study design We reviewed the North American Shwachman–Diamond Syndrome Registry. Genetic reports of biallelic Shwachman–Bodian–Diamond syndrome mutations confirming the diagnosis of SDS were available for 37 patients.

Results Neutropenia was the most common hematologic abnormality at presentation (30/37, 81%); however, only 51% (19/37) of patients presented with the classic combination of neutropenia and steatorrhea. Absence of pancreatic lipomatosis on ultrasound or computed tomography scan, normal fecal elastase levels, and normal skeletal survey do not rule out the diagnosis of SDS. SDS was diagnosed in 2 asymptomatic siblings of SDS probands. Twenty-four of 37 patients (65%) had congenital anomalies.

Conclusion Our cohort reveals a broad range of clinical presentation for SDS. Clues to the underlying diagnosis of SDS included cytopenias with a hypocellular marrow, congenital anomalies, family history, and myelodysplasia with clonal abnormalities frequently found in SDS. Reliance on classic clinical criteria for SDS would miss or delay diagnosis of a significant subset of patients with SDS. *(J Pediatr 2014;164:866-70)*.

Shwachman–Diamond syndrome (SDS) is an autosomal recessive disorder characterized by congenital anomalies, exocrine pancreatic dysfunction, bone marrow failure, and predisposition to myelodysplasia (MDS) and leukemia, particularly acute myeloid leukemia (AML).[1] Previous studies have found mutations in the Shwachman–Bodian–Diamond syndrome (*SBDS*) gene located on chromosome 7q11, which can be found in approximately 90% of classically presenting patients with SDS. *SBDS* encodes an evolutionarily conserved protein, which functions in ribosomal maturation as well as being implicated in additional cellular functions.[2-4] SDS is a multi-system disorder with potential manifestations in the skeletal, hepatic, cardiac, immune, and central nervous systems.[5]

Prior to the identification of the *SBDS* gene, SDS was diagnosed on the basis of clinical criteria consisting of the combination of marrow failure (typically manifested by neutropenia) and exocrine pancreatic dysfunction.[5,6] With the advent of genetic testing for *SBDS* mutations, the range of SDS clinical phenotypes can now be explored. A recent case report of 2 patients with unusual presentations of SDS highlighted the need for a systematic evaluation of patients with SDS.[7]

To investigate cryptic presentations of SDS, we conducted a retrospective review of medical records from the North American Shwachman–Diamond Syndrome Registry (SDSR). Data were extracted from clinic notes and from laboratory, pathology, and radiology reports. The SDSR was established in 2008 to elucidate the clinical spectrum, natural history, and molecular pathogenesis of SDS with the goal of improving diagnosis and therapy. The SDSR also provides an educational resource for patients, families, and healthcare providers. This registry is a collaborative effort between the Fred Hutchinson Cancer Research Center in Seattle, Washington, and Cincinnati Children's Hospital Medical Center in Cincinnati, Ohio, and works in partnership with the Severe Chronic Neutropenia International Registry at the University of Washington, in Seattle, Washington.

In this report, we investigate the initial clinical presentations of patients with genetically-confirmed SDS in the North American SDSR. We found a broad range of clinical presentations for SDS, and identified several features providing clues to the underlying diagnosis of SDS.

AML	Acute myeloid leukemia
CT	Computed tomography
MDS	Myelodysplasia
SBDS	Shwachman–Bodian–Diamond syndrome
SDS	Shwachman–Diamond syndrome
SDSR	Shwachman–Diamond Syndrome Registry

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Methods

The study was a retrospective review of medical records including clinic notes, laboratory reports, pathology reports, and radiology reports collected through the SDSR. Informed consent was obtained in accordance with the study protocol approved by the Institutional Review Boards of the Fred Hutchinson Cancer Research Center and Cincinnati Children's Hospital Medical Center. This report was limited to patients with *SBDS* gene mutations confirmed by review of the genetic testing reports. Neutropenia was defined as absolute neutrophil count $\leq$1500/μL on at least 3 separate occasions, anemia as hemoglobin below the age-related normal range, and thrombocytopenia as platelet count $\leq$150 000 platelets/μL in the absence of other apparent etiologies for cytopenias.[6] Pancreatic insufficiency was defined as pancreatic isoamylase and/or trypsinogen below reference for age, or fecal elastase <100 μg/g stool. Isoamylase was not utilized in patients <3 years of age because of the age-dependent nature of isoamylase production, resulting in low levels in healthy children under 3 years of age.[8] Similarly, trypsinogen was not utilized in patients >3 years of age because of the frequent normalization of trypsinogen with increasing age.[8] Telomere length measurements were performed by Repeat Diagnostics Inc (Vancouver, British Columbia, Canada).[9]

Results

The study subjects included 37 patients in the SDSR with genetic test reports confirming the presence of mutations in the *SBDS* gene (**Table I**). The SDS study cohort included 24 male and 13 female patients. Median patient age at clinical presentation was 3.5 years with a range of 0.02-18 years (**Table II**). The classic presentation of neutropenia associated with diarrhea was seen in only 19/37 (51%) of patients. One patient presented with isolated neutropenia without any history of diarrhea, failure to thrive, or congenital anomalies. Two patients presented with diarrhea without neutropenia. Three patients presented with failure to thrive without diarrhea or neutropenia. The absence of neutropenia or diarrhea at presentation does not rule out the diagnosis of SDS. It should also be noted that neutropenia may be intermittent and may develop over time.

Neutropenia (absolute neutrophil count <1500/μL), occurring in 81% (30 of 37 patients), was the most common hematologic abnormality at clinical presentation. Three patients presented with severe anemia requiring transfusion support together with neutropenia or pancytopenia. Strikingly, 5 patients (14%) came to medical attention with no history of cytopenias.

Non-classical presentations were also noted in several other patients. One patient presented with isolated mild thrombocytopenia at age 12 years with the initial diagnosis of hypocellular MDS with a del 20(q) cytogenetic clone without any history of steatorrhea or failure to thrive or cytopenias. Another proband presented at age 17 years without cytopenias or steatorrhea, but with a family history of a sibling who died from AML at age 20 years. Fatty pancreatic changes were noted in this sibling post-mortem and *SBDS* testing of the living proband was positive for *SBDS* mutations. Upon diagnosis, a bone marrow exam revealed clonal changes which subsequently progressed to MDS. Another SDS proband had an asymptomatic sibling with normal stature and lacking a history of diarrhea; this sibling was subsequently found to carry the same *SBDS* mutations as the proband and the blood count showed red cell macrocytosis. One subject had very short telomeres (<1st percentile for age) across 3 lymphocyte subsets as well as in total lymphocytes (**Figure**), a pattern more typically associated with dyskeratosis congenita. This subject did have testing for mutations in dyskeratosis congenita 1 (*DKC1*), the most common gene affected in dyskeratosis congenita, and was negative.

Table I. *SBDS* genetic mutations

Patient number (n = 37)	*SBDS* mutations
25	258+2 T>C and 183_184 TA>CT
5	Homozygous 258+2 T>C
2	Homozygous 258+2 T>C and 183_184 TA>CT
1	258+2 T>C and IVS2-2 A>G
1	258+2 T>C and F57S (TTT>TCT)
1	258+2 T>C and 18 delC
1	258+2 T>C and 120 del G
1	258+2 T>C and Q153R (458 A>G)

Bone marrow evaluations revealed hypocellularity for age in all 32 patients evaluated. Dysplasia was noted in 27 of 31 evaluable records. Marrow dysplasia was most significant in the myeloid lineage in 22 of 31 patients, although erythroid and megakaryocytic involvement were noted in 11 and 8 cases respectively. Seven of 31 patients demonstrated cytogenetic clones with del 20q noted in 5/37 subjects. Three of these patients had complex clonal abnormalities of whom 2 are alive and well after hematopoietic stem cell transplant and 1 remains stable with observation.

Twenty-seven of 37 patients (73%) presented with failure to thrive. Only 21/37 patients (58%) had a history of diarrhea. Radiologic reports of pancreatic imaging studies were available for 24 patients; Seventeen patients had pancreatic ultrasound reports available. Of these, 14 had pancreatic lipomatosis noted on ultrasound. One patient initially had a normal pancreatic ultrasound at age 2.6 years, but pancreatic lipomatosis was noted on a subsequent ultrasound 3 years later. One patient had an initial pancreatic ultrasound that reported lipomatosis but a subsequent ultrasound report did not comment on pancreatic lipomatosis. Two patients had no pancreatic lipomatosis noted on ultrasound; 1 of these patients had a small pancreatic size. Two patients had ultrasound reports that lacked any comments regarding the pancreas. Ten patients had computed tomography (CT) reports available. Pancreatic lipomatosis was noted in 9 patients. For 1 patient, an initial CT scan showed a small pancreas without lipomatosis at

Table II. Clinical presentation of SDS

UPN	Sex	Neutropenia	Diarrhea	Failure to thrive	Congenital anomalies	Thrombocytopenia	Anemia
1	Male	+	+	+	+		
2	Female	+	+	+	+		
3	Female	+		+		+	
4	Male	+	+	+	+		
5	Male	+		+	+		
6	Male	+			+		+ (txn)
7	Female	+	+	+		+	+
8	Male			+	+		
9	Male	+	+	+			
10	Male	+	+		+		
11	Female		+				
12	Male					+	
13	Male	+	+	+	+		
14	Female	+	+	+	+		
15	Male	+	+	+	+		
16	Male	+	+	+	+	+	+ (txn)
17	Female	+	+	+	+		
18	Male	+	+	+	+		
19	Female	+	+	+	+	+	
20	Female	+	+	+	+		
21	Male	+					+(txn)
22	Female			+			
23	Male		+	+			
24	Male			+	+		
25	Male				+	+	
26	Male	+			+		
27	Female	+		+	+		+
28	Female	+		+	+	+	+
29	Male	+	+	+	+		
30	Male	+		+			
31	Male	+	+	+			
32	Male	+			+	+	
33	Male	+				+	
34	Female	+	+	+	+	+	
35	Male	+	+	+	+		
36	Female	+	+	+			
37	Male	+					

UPN, study code for patient; *txn*, transfusion-dependent.

age 1.3 years but a subsequent CT scan showed pancreatic lipomatosis 4 years later. The pancreas was small or atretic for 5 patients and enlarged for one. One patient had pancreatic lipomatosis noted by magnetic resonance imaging.

Fourteen of 17 patients tested (82%) had low fecal elastase levels (<100 ug/g wet stool), and 3 had normal fecal elastase levels. Two of the 3 patients with normal levels were on pancreatic enzyme supplements at the time the fecal elastase levels were evaluated but 1 patient had normal fecal elastase levels without pancreatic enzyme supplements. Either serum trypsinogen (age <3 years) or pancreatic isoamylase (age >3 years) were low in all 17 patients tested.

Twenty-four of 37 patients (65%) had congenital or endocrine anomalies (Table III). Skeletal abnormalities were the most common abnormality reported in 38% of patients, either noted on physical exam or by skeletal survey. A wide variety of congenital anomalies involving the cardiac, gastrointestinal, renal, neurologic, urologic, and other systems were reported.

Discussion

Prior to the advent of genetic testing, the diagnosis of SDS was based largely on the clinical criteria of neutropenia and exocrine pancreatic insufficiency. We studied the presenting clinical phenotypes of 37 patients with genetically confirmed SDS and discovered an unexpectedly broad range in clinical phenotype at presentation. The frequency of cryptic presentations of SDS raises the likelihood that SDS is an underdiagnosed disorder. Serum trypsinogen and pancreatic isoamylase were the most sensitive measures of clinically asymptomatic pancreatic dysfunction in SDS. Normal pancreatic imaging studies and normal fecal elastase do not rule out the diagnosis of SDS.

The timely diagnosis of SDS carries implications for medical management and treatment. Routine monitoring of blood counts and marrow cytogenetics will allow early detection of marrow failure and transformation to MDS, preventing progression to AML. The incidence of AML in SDS ranges from 18% to 36% over 20-30 years[1], and often those who do progress to AML are older. Severe marrow failure, MDS, or leukemia are treated with a hematopoietic stem cell transplant. Patients with SDS require reduced intensity conditioning regimens to avoid undue regimen-related toxicities; thus, the prior recognition of the underlying diagnosis of SDS is critical.[10,11] Transplant outcomes are superior if initiated prior to the development of leukemia, so regular monitoring of the blood and bone marrow are of

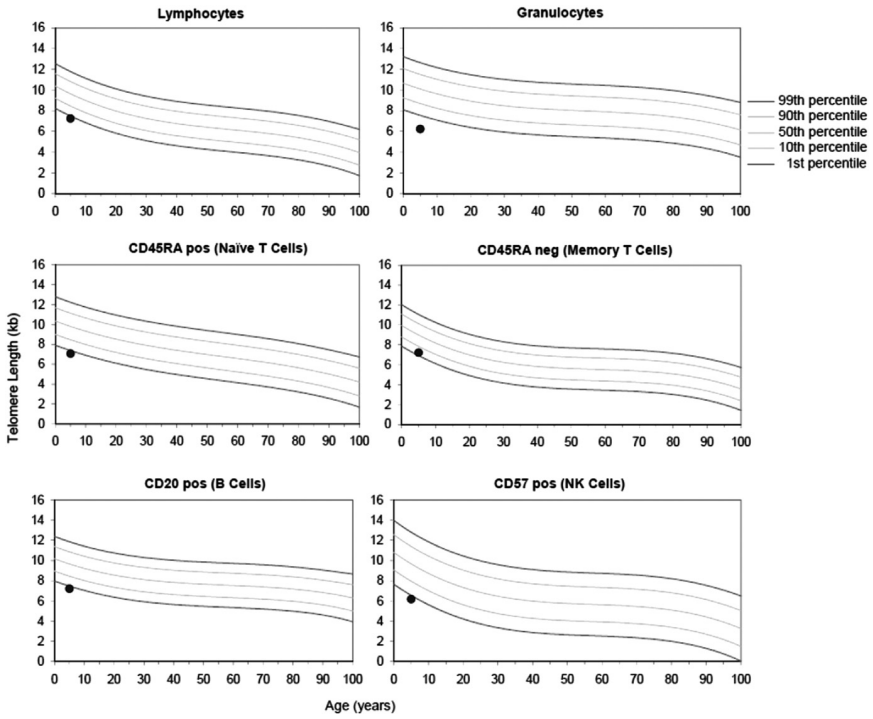

Figure. Extremely short telomeres in a patient with SDS. Telomeres were noted to be <1st percentile for age across 3 lymphocyte subsets as well as in total lymphocytes.

great value. The diagnosis of SDS also permits genetic testing of potential sibling donors prior to transplant, particularly key if the sibling is the stem cell donor.

It is important to note that hematologic abnormalities such as cytopenias, marrow hypocellularity, and marrow dysplasia are not static but evolve over time even if absent at initial presentation. Similarly, skeletal abnormalities may evolve over time. Our study demonstrates that the absence of these findings at presentation does not rule out the diagnosis of SDS. In our cohort of patients with genetically-confirmed SDS, 31/31 marrows examined were hypocellular for age. Normocellular or hypercellular marrows have been reported in the literature for patients diagnosed with SDS on clinical grounds prior to the availability of genetic testing. Given the clinical overlap between SDS and other marrow failure syndromes, further study of the range of marrow abnormalities in patients with SDS with or without *SBDS* mutations is of high interest.

The differential diagnosis of neutropenia presenting without diarrhea is broad, and SDS is a rare disorder. Clues to cryptic presentations of SDS in our cohort included bone marrow hypocellularity, mild marrow dysmorphologies, congenital anomalies, family history of SDS, and the del20q clonal marrow abnormality. *SBDS* genetic testing should be considered for patients with idiopathic hypoproductive cytopenias together with any of these additional features.

This study raises the importance of genetic testing of clinically asymptomatic siblings of SDS probands. Furthermore, the diagnosis of SDS should also be considered in adults because cryptic presentations may be missed during childhood. Thus far, the Registry has not found any reports of aplastic anemia arising in obligate *SBDS* heterozygotes such as parents or grandparents.

It is important to emphasize that the absence of a gene mutation does not rule out the diagnosis of SDS. Although 90% of patients with classically presenting SDS have mutations in the *SBDS* gene, there remain a proportion of patients with clinically diagnosed SDS without known mutations. However, it is currently unclear whether these *SBDS* mutation-negative patients represent a different genetic variant of SDS or instead might constitute a mixture of different undefined disorders with overlapping clinical features. Therefore, this analysis was restricted to patients with *SBDS* mutation-positive SDS. Additional studies are necessary to further characterize these *SBDS* mutation-negative patients both clinically and molecularly.

Current diagnosis and management of SDS is largely based on case series and consensus reports, as its natural history remains poorly characterized because of the rarity of this disease. Controlled clinical studies to inform diagnosis and therapy of SDS are lacking. Although this study represents a large cohort of patients with SDS evaluated for initial presentation, the small size of the current registry cohort remains a limitation that should be considered in interpretation. Longitudinal cohort studies stand to better delineate diagnostic criteria, phenotypic range, complications, and treatment outcomes to improve the medical care of patients

Table III. Congenital anomalies and medical comorbidities identified in patients with SDS

	Number of patients (n = 37)
Congenital anomalies	
Cardiac	7 (19%)
Ventricular septal defect	3
Patent foramen ovale/atrial septal defect	5
Patent ductus arteriosus	5
Gastrointestinal	3 (8%)
Malrotation	1
Bilateral inguinal hernia	1
Imperforate anus	1
Musculoskeletal	14 (38%)
Thoracic dystrophy (rib abnormalities)	9
Short arms/legs	2
Metaphyseal dysplasia	4
Other legs (knock knees, bowing legs)	2
Pelvic dysostosis - absent pubic ramus	1
Scoliosis	3
Neurologic	2 (5%)
Chiari malformation, type I	1
Cerebellar tonsillar ectopia	1
Myopathy/hypotonia	1
Urologic	2 (5%)
Testicular atrophy	2
Hypospadias	1
Other	5 (14%)
Subglottic stenosis	1
Eye anomaly	1
Ear anomalies/hearing loss	4
Medical comorbidities	
Eczema	11
Elevated liver function tests	15
Adrenal insufficiency	1
Hypopituitarism	1
Type I diabetes	1
Pulmonary hypertension	1
Hypothyroid	1

with SDS. This study highlights the continued importance of systematic study through registries for rare disorders. ■

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