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Clinical and Molecular Pathophysiology of Shwachman–Diamond Syndrome: An Update

Kasiani C. Myers, MD[a,*], **Stella M. Davies, MBBS, PhD, MRCP**[b], and **Akiko Shimamura, MD, PhD**[c]

[a]Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, University of Cincinnati, 3333 Burnet Avenue, MLC 7015, Cincinnati, OH 45229, USA

[b]Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, University of Cincinnati, 3333 Burnet Avenue, Cincinnati, OH 45229, USA

[c]Department of Pediatric Hematology/Oncology, Fred Hutchinson Cancer Research Center, Seattle Children's Hospital, University of Washington, 4800 Sand Point Way NE, Seattle, WA 98105, USA

SUMMARY

Many exciting advances in our understanding of SDS have occurred in the past few years; however, our understanding of the natural history and spectrum of disease, diagnosis, and therapy remain limited. Ongoing basic and clinical investigations on larger numbers of patients are crucial to better tie together our evolving comprehension of molecular function and clinical manifestations of this multiorgan disease to affect the treatment of patients with this rare disorder.

Keywords

Bone marrow failure; Shwachman–diamond syndrome; Ribosomes

INTRODUCTION

Shwachman–Diamond syndrome (SDS) is a rare autosomal recessive multisystem disorder characterized by congenital anomalies, exocrine pancreatic dysfunction, bone marrow failure, and predisposition to myelodysplasia (MDS) and leukemia, particularly acute myeloid leukemia (AML). In addition, growth, heart, liver, central nervous system, skeletal system, and the immune system may also be affected. The incidence of SDS is indirectly approximated at 1:77,000.[1] Around 90% of patients with SDS harbor mutations in the Shwachman-Bodian-Diamond syndrome (*SBDS*) gene located on chromosome 7q11. SBDS encodes a novel protein involved in ribosomal maturation and implicated in additional functions, such as cell proliferation and mitosis,[2] as well as in the stromal microenvironment.[3,4]

*Corresponding author. kasiani.myers@cchmc.org.

Although the majority (90%)[5] of patients clinically diagnosed with SDS harbor mutations in the *SBDS* gene, phenotype varies widely between patients and even within the same individual over time, posing challenges for diagnosis and treatment. Owing to the rarity of this disorder, the natural history of SDS remains poorly defined and controlled clinical studies to direct therapy are lacking. Thus, current management is largely based on case series and consensus reports. Longitudinal clinical studies are needed to define the diagnostic criteria, phenotypic range, and molecular pathophysiology of SDS to identify risk factors for medical complications and guide therapeutic interventions.

This review highlights recent advances in the understanding of the clinical manifestations and molecular pathogenesis of SDS. The reader is referred to prior excellent reviews for a general overview of SDS.[6–8]

CLINICAL MANIFESTATIONS

Owing to the rarity of this syndrome, our understanding of the full spectrum of clinical disease in SDS remains incomplete. The current knowledge was summarized recently in an updated clinical consensus guideline.[6] The classical clinical scenario describing SDS includes exocrine pancreatic dysfunction and bone marrow failure (Box 1). Skeletal abnormalities may include metaphyseal dysplasia, flared ribs, thoracic dystrophies, and osteopenia.[9] Neurocognitive deficits have been described.[10] While the exocrine pancreatic dysfunction in SDS is well described, a distinctive abnormal hepatic phenotype in these patients has also been reported.[11] Progression and evolution of bone marrow disease remains a major source of morbidity and mortality in these patients.[12,13] Registries and clinically annotated biosample repositories for SDS are poised to expand our knowledge of this disease and its myriad of developmental effects through systematic and longitudinal studies leading to more disease-specific interventions.

HEMATOLOGIC MANIFESTATIONS

Patients with SDS are at risk for cytopenias secondary to marrow failure. Neutropenia is reported in 88% to 100% of patients and can be either intermittent or persistent, with variable severity. Anemia and thrombocytopenia have also been reported in most patients, although both are often intermittent or asymptomatic. Elevated hemoglobin F levels can also be seen in a subset of patients.[14,15] Severe aplastic anemia with trilineage cytopenias may also develop in a subset of patients. The French Severe Chronic Neutropenia Registry recently evaluated the hematologic complications in their cohort of 102 genetically diagnosed patients with SDS and found 41 patients (40%) with hematologic complications including transient severe cytopenias.[12] Of these patients, 21 (20.6%) presented with definitive persistent cytopenias (anemia with hemoglobin levels <7 g/dL or profound thrombocytopenia with platelets <20 g/L), in 9 of whom the condition was classified as malignant and in another 9 as nonmalignant, and in 3, the condition progressed from nonmalignant to malignant. Prognostic factors reported with severe cytopenias in this cohort included early age at diagnosis and hematologic parameters.

Reports of progression to MDS or AML in patients with SDS have varied. Previously, the Severe Chronic Neutropenia International Registry (SCNIR) had reported a rate of 1% per year of MDS or AML in patients with SDS, with an overall incidence of 8.1% in 37 patients with SDS in 10 years.[16,17] The French registry reported a rate of transformation to MDS or AML of 18.8% at 20 years and 36.1% at 30 years in a cohort of 55 patients with SDS.[18] Some of this discrepancy arises from differences in the definition of MDS. More recently, the Canadian Inherited Bone Marrow Failure Study (CIBMFS) registry reported a cumulative transformation rate of 18% in 34 patients with SDS.[13] This result is in contrast to other recent reports from the NIH registry (17 patients) and the Israeli registry (3 patients) in which no patient developed MDS or AML.[19,20] Although it is difficult to draw conclusions from such small numbers of patients, this discrepancy may be partly due to the age of these cohorts. The median age of transformation for patients with SDS was 19.1 years in the French group and 20 years in the Canadian cohort, whereas the NIH and Israeli cohorts had median ages of 14 and 4 years, respectively, at the time of report.[13] Transformation rates reported by the SCNIR for patients with severe congenital neutropenia (SCN) are 11.8% at 10 years, whereas the rates for fanconi anemia (FA) and dyskeratosis congenita (DC) by the age of 50 years as reported by the NIH are 40% and 30%, respectively, for myelodysplasia (MDS), and 10% for both for AML.[17,19] The Diamond Blackfan Anemia Registry reports that patients with diamond blackfan anemia (DBA) are less likely to transform with cumulative incidence of AML of 5% by the age of 46 years, with incidence increasing only after the age of 40 years.[21] Together, these data suggest that the risk of malignant transformation in patients with SDS is significant, especially with respect to some of the other inherited marrow failure syndromes, but occurs with less frequency and longer latency than in patients with Fanconi anemia. Published reports of solid tumors in patients with SDS are rare thus far. There are only 2 cases in the literature, one of bilateral breast cancer[22] in a 30-year-old woman with SDS and another of dermatofibrosarcoma in a 20-year old-woman, which had been present and slowly growing for approximately 3 years at diagnosis.[23]

It has long been known that patients with SDS may develop characteristic cytogenetic clones in the absence of overt MDS or AML and that these abnormalities may persist over time without progression or malignant evolution. Recent reports suggest that a common cytogenetic abnormality seen in patients with SDS, del(20)(q11), is not associated with a high risk of malignant transformation.[24,25] Another characteristic cytogenetic anomaly in SDS that can come and go over years of time without progression to MDS/AML is isochromosome i(7)(q10).[26] Maserati and colleagues[25] reported on clonal changes in 22 new patients with SDS and 14 cases of follow-up of previously reported cases.[25] Of the 36 cases, 16 demonstrated clonal changes, all of which involved either chromosome 7 or 20. Chromosome 7 abnormalities included isochromosome [i(7)(q10) (n = 10)], [add(7)(p?) (n = 1)], and a long arm deletion [del(7)(q22q23) (n = 1)]. All 6 clones involving chromosome 20 abnormalities initially involved del(20)(q11); however, 2 evolved into subclones, which had acquired additional cytogenetic abnormalities. All 5 patients with del(20)(q11) demonstrated loss of the common MDR established in patients with MDS who did not have SDS. Over the course of the study (range of follow-up being between 1 month and 9 years), 8 patients had stable clones, 4 demonstrated increasing clonal involvement, and 1 had diminished clonal involvement, irrespective of the initial type or size of clonal abnormality. Despite these

additional cytogenetic abnormalities and the loss of a region commonly deleted in MDS/AML, the only patient to progress to MDS or require bone marrow transplantation carried the add(7)(p?) abnormality, and no patient progressed to AML. In addition, the appearance of clonal abnormalities seemed to be age related, with increased frequency of clonal changes seen with increasing age.

Furthermore, Crescenzi and colleagues[24] evaluated the bone marrows of 2 patients with SDS and del(20)(q11) who had been followed up over a 6- to 7-year period without development of MDS/AML. In these patients, there was no acquisition of additional cytogenetic changes associated with MDS/AML despite increasing clonal population in 1 patient. By fluorescence in situ hybridization, del(20)(q11) was seen to be present in totipotent hematopoietic stem cells as well as downstream myeloid and lymphoid lineages, indicating preservation of the capacity to differentiate even in the face of this cytogenetic abnormality.

Historically, clinical observations have also demonstrated an increased frequency of infection beyond that attributable to simple neutropenia in patients with SDS. Sepsis is one of the most common fatal infections in SDS, often associated with neutropenia. However, patients with SDS also have susceptibility to recurrent bacterial, viral, and fungal infections.[27] Dror and colleagues[28] prospectively studied immune functions in this population. B-cell defects (less number of circulating B cell, low levels of IgG and IgG subclasses, and deficient antibody production) and T-cell defects (low $Cd3^1$/$CD4^1$ cell subpopulations and decreased T-lymphocyte proliferation) were described in most patients with SDS studied. Universally abnormal neutrophil chemotaxis was also reported as described previously.[29,30] However, in contrast to other neutrophil chemotaxis disorders, patients with SDS retain the ability to form purulent abscesses and empyema.[27]

GASTROINTESTINAL MANIFESTATIONS

Exocrine pancreatic dysfunction is a classic feature of SDS resulting from severe depletion of pancreatic acinar cells.[14,31] The majority (>90%) of patients with SDS are diagnosed with pancreatic dysfunction in the first year of life, often in the first 6 months. Clinical manifestations range widely from severe dysfunction with significant nutrient malabsorption, steatorrhea, and resultant failure to thrive, to completely asymptomatic. Despite these findings, clinical symptoms in many patients with SDS spontaneously improve with age for reasons that remain unclear. In as many as 50% of patients, pancreatic enzyme supplementation can be stopped by the age 4 years based on evidence of normal fat absorption, although enzyme secretion deficits remain.[32] A recent study of parotid acinar function in 16 patients with SDS compared with 13 healthy controls and 13 patients with cystic fibrosis or fibrosing pancreatitis found parotid acinar dysfunction.[33] Both serum pancreatic and parotid isoamylase levels were lower in patients with SDS than in healthy controls, whereas pancreatic isoamylase levels were lower in other disease controls than in normal controls. Secreted parotid amylase levels were also lower in patients with SDS than in healthy controls, whereas the levels in disease controls were comparable to those in normal controls. These findings suggest a more generalized defect in acinar cell function in patients with SDS. In addition, a recent study by Shah and colleagues[34] of histologic changes in gastrointestinal mucosal biopsies of 15 symptomatic patients with genetically

confirmed SDS demonstrated that more than 50% showed varying degrees of duodenal inflammation by histology. This result suggests that there may be an enteropathic component in addition to the pancreatic exocrine failure contributing to the symptoms in some patients with SDS.

Although the pancreatic manifestations of SDS are well known, patients with SDS often have other gastrointestinal involvement, most notably in the liver. A recent longitudinal study of 12 Finnish patients with SDS further characterized the hepatic manifestations of SDS,[11] confirming previous reports of elevated levels of transaminases and hepatomegaly in younger patients with SDS that resolve with age. In addition, this study found that a majority (58%) of patients had elevated levels of bile acids. Of these patients, 3 had longitudinal bile acid measurements, and all had repeatedly elevated levels, although intermittently in 2, raising the concern for persistent cholestasis. Longitudinal examination of hepatic imaging revealed hepatomegaly only in young patients (younger than 3 years). Interestingly, all 3 patients older than 30 years had developed hepatic microcysts that were readily apparent on imaging studies.

SKELETAL MANIFESTATIONS

Skeletal dysplasias are also a frequent manifestation of SDS. The characteristic findings in SDS include short stature as well as delayed appearance of normally shaped epiphyses and progressive metaphyseal thickening/dysplasia in the long bones and costochondral junctions. In a group of 15 individuals with genetically confirmed SDS, Makitie and colleagues[9] demonstrated skeletal abnormalities in all individuals, although they were variable in severity and location, often evolving with age.

In a recent study, Toiviainen-Salo and colleagues[35] demonstrated that SDS is also associated with low-turnover osteoporosis. A total of 11 individuals with genetically confirmed SDS were evaluated and 10 were found to have abnormalities of bone health, including markedly reduced bone mineral density by Z-scores, with 3 individuals also demonstrating vertebral compression fractures. Mild vitamin D deficiency was present in 6 individuals, 3 with secondary hyperparathyroidism, while vitamin K deficiency was also found in 6 individuals, both of which are known to play an important role in skeletal health.

NEUROCOGNITIVE MANIFESTATIONS

Historically, patients with SDS have been shown to have neurocognitive impairment as well as structural brain alterations.[36,37] In a recent study, Kerr and colleagues[10] reported on the neuropsychological function in 34 children with SDS, comparing them to 13 sibling controls as well as 20 patients with cystic fibrosis matched for age and gender. Patients with SDS ranged widely in their abilities compared with controls, from severely impaired to superior in some areas measured. Overall, this study found that patients with SDS may have significant impairments in perceptual skills including reasoning and visual-motor skills, higher-order language, intellectual reasoning, and academic achievement. About 20% of patients with SDS were found to have an intellectual disability, with perceptual reasoning being particularly difficul. Furthermore, children with SDS were 10 times more likely to be

diagnosed with pervasive developmental disorder (6%) than the general population (0.6%). In addition, both patients with SDS and their siblings were more likely to have attention deficits than patients with cystic fibrosis. These findings were not associated with secondary complications of SDS, sex, or age. It has therefore been postulated that *SBDS* may have a role in neurodevelopment, especially because many patients with SDS have abnormalities on neuroimaging. These findings also emphasize the importance of early neurocognitive assessment and intervention in patients with SDS.

DIAGNOSTIC APPROACH AND MANAGEMENT

Although the clinical diagnosis of SDS is often made in the first few years of life, typically with the classic presentation including failure to thrive, associated feeding difficulties, and variable recurrent or excessive infections, many patients may be diagnosed later in childhood or even adulthood, especially those with more mild pancreatic phenotype. It is important to recognize that older patients may present at a stage when pancreatic dysfunction is no longer evident, and thus a high index of suspicion may be warranted. The diagnostic workup continues to evolve, and the diagnosis is currently made clinically based on evidence of pancreatic dysfunction and hematologic abnormalities (see Box 1). Approximately 90% of patients with SDS have a biallelic mutation in the *SBDS* gene, leaving 10% without known molecular cause. It is important to consider other common causes of pancreatic dysfunction including cystic fibrosis, which can be ruled out with a sweat chloride test, as well as other inherited marrow failure disorders including Pearson disease, which includes pancreatic dysfunction, cytopenias, and bone marrow ring sideroblasts.

Patients with SDS require thorough screening for associated complications both at diagnosis and subsequently at regular intervals throughout their care. Recommended evaluations are listed in Table 1. Regular complete blood cell counts and bone marrow evaluations should be emphasized to monitor for the evolution of marrow dysfunction or malignant transformation, regular nutritional and growth assessments, as well as neurodevelopmental evaluations. Genetic counseling should be made available to patients as well as family members.

Surveillance as described above and supportive care for the complications of SDS are critical for the medical management of patients with SDS. Pancreatic enzyme supplementation should be administered to those with evidence of pancreatic insufficiency. Although many patients with SDS manifest varying degrees of cytopenias, regular transfusion requirements are rare outside the setting of severe aplastic anemia. Although neutropenia is common, it is typically intermittent and often mild to moderate in severity, thus most patients do not require treatment with granulocyte colony stimulating factor (GCSF). Chronic therapy with GCSF should be contemplated in the case of recurrent invasive bacterial/fungal infections with concomitant severe neutropenia, with the goal of infection prevention. Individual patients may require only an intermittent schedule of GCSF or may need continuous daily treatment.

Hematopoietic stem cell transplantation (HSCT) should be considered for the treatment of severe aplastic anemia and is the treatment of choice for progression to MDS or AML in

patients with SDS. Chemotherapy can be used as a bridge to HSCT in AML secondary to SDS; however, prolonged complete remission remains elusive with chemotherapy alone in SDS, and thus urgent use of HSCT is warranted. Historically, outcomes in MDS or AML in SDS after transplantation lag behind those of severe aplastic anemia, emphasizing the importance of regular surveillance with blood counts and bone marrow examinations.[38]

MOLECULAR PATHOPHYSIOLOGY

The SBDS protein has been associated with critical cellular pathways including ribosomal biogenesis,[39–42] microtubule stabilization,[2] and actin polymerization.[43,44] More recently, further murine studies suggest novel functions in stromal effects on the marrow microenvironment.[3,4]

SBDS AND RIBOSOMAL BIOGENESIS

Recent studies have further identified the structure of SBDS and provided additional insights into its interaction with RNA. The crystal structure of *Methanothermobacter* SBDS was elucidated to a 1.75 Å resolution by Ng and colleagues,[39] and the structure of human SBDS was determined by solution nuclear magnetic resonance. Supporting the interaction of SBDS in ribosome function, the localization of the SBDS protein to the nucleolus of human cells depends on active ribosomal RNA transcription, as evidenced by its diminution with low-dose actinomycin D, an RNA polymerase I inhibitor. SBDS-deficient lymphoblasts from patients with SDS are hypersensitive to actinomycin D, which can be abrogated with the addition of wild-type SBDS cDNA, supporting an underlying impairment of ribosome biogenesis. In keeping with yeast models, SBDS also associates with the large 60S ribosomal subunit, although a consistent defect in ribosomal RNA processing in fibroblasts of patients with SDS was not demonstrated.[40] SBDS was also demonstrated to associate with multiple ribosomal proteins in HEK293 cells including RPL3, RPL4, RPL6, RPL7, RPL7A, and RPL8, as well as nucleolin and nucleophosmin.[45] Mutations in *Tif6*, the yeast *eIF6* ortholog, rescue the slow growth phenotype of yeast deficient in the *SBDS* ortholog *Sdo1*.[46] In recent work by Finch and colleagues,[41] the crucial role of SBDS in ribosome biogenesis was further shown through its interaction with the GTPase elongation factor-like 1 (EFL1) in mice. This interaction results in the coupling of GTP hydrolysis by ELF1 to the release of EIF6 from the pre-60S ribosome subunit in an SBDS-dependent manner. eIF6 functions in 60S subunit biogenesis,[47,48] and its association with the nascent 60S subunit sterically prevents its association with the 40S subunit.[49,50] These data support a model whereby SBDS facilitates the joining of the 60S subunit to the 40S subunit for active translation through the formation of the active 80S ribosome.[41] The conservation of this function was later confirmed in *Dictyostelium* species.[42]

SBDS AND STROMAL MICROENVIRONMENT

Involvement of SBDS in both bone marrow hematopoietic and stromal cell functions has been demonstrated previously.[15] Recent work by Raaijmakers and colleagues[3] has revealed new insights into the role of SBDS in bone marrow stromal cells. Targeted deletion of *Dicer1*, an RNAIII endonuclease essential for microRNA biogenesis and RNA processing, in

mouse osteoprogenitors resulted in reduced expression of *Sbds*, along with disrupted hematopoiesis with subsequent development of MDS and AML. Acquisition of several genetic abnormalities occurred despite intact *Dicer1*. Subsequent deletion of *Sbds* in mouse osteoprogenitors also induced bone marrow dysfunction with leukopenia, lymphopenia, and MDS, along with bony abnormalities, mimicking clinical disease.[3] In addition, microarray expression analysis of human SBDS knockdown cell lines by Nihrane and colleagues[4] reveal increased expression of osteoprotegerin and vascular endothelial growth factor-A, which are known to have effects on osteoclast differentiation, angiogenesis, and monocyte/macrophage migration. These data suggest that changes in the hematopoietic microenvironment due to decreased SBDS expression in stromal cells may play a role in promoting MDS and malignant transformation.

SBDS AND GENOMIC INSTABILITY

Evidence pointing toward an additional role for SBDS outside of ribosomal biogenesis and the stromal environment has also been demonstrated. Austin and colleagues[2] demonstrated that SBDS can be localized to the mitotic spindle of primary human bone marrow stromal cells. They were also able to show that lymphocytes and fibroblasts from patients with SDS have an increased number of multipolar spindles during cell division, generating increased genomic instability. Orelio and colleagues[43,44] demonstrated colocalization of SBDS with microtubules and the centromeres of the mitotic spindle, as well as the microtubule organizing center in interphase neutrophils. They were able to show decreased SBDS expression during neutrophil differentiation both in a human myeloid leukemia cell line and in primary human CD341 cord blood progenitor cell cultures, as well as differential proliferation and differentiation of neutrophils in SDS cultures compared with that of controls.[43,44] Together, these studies suggest a role for SBDS in cell proliferation and cell division in the myeloid compartment, which may be reflected by the clinical phenotype of neutropenia and risk of malignant transformation in SDS.

OTHER MOLECULAR FUNCTIONS

Additional roles for SBDS have also been recently highlighted. Investigations by Ball and colleagues[45] suggest an involvement in DNA metabolism by demonstrating that FLAG (fludarabine, cytosine arabinoside, and granulocyte-colony stimulating factor)-tagged human SBDS copurifies with proteins implicated in DNA metabolism such as replication protein A1 (RPA1), DNA-dependent protein kinase (DNA-PK), histones, and X-ray repair cross-complementing protein 5 (XRCC5). Orelio and Kuijpers[43] also revealed a role for SBDS in actin-dependent cellular activities by showing that it colocalizes with F-actin and Rac2 in cellular protrusions of activated and adherent neutrophils from patients with SDS as well as a leukemic cell line. F-actin polymerization is also altered and polarization is delayed in these patient-derived neutrophils, perhaps indicating a role in actin-related processes, as reflected by their impaired chemotaxis.

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Box 1

Clinical and molecular diagnostic features of Shwachman–Diamond syndrome

Biallelic mutations in SBDS or clinical Shwachman–Diamond syndrome: one criteria from Category I and II

Category I

Low levels of trypsinogen (age <3 years) or low pancreatic isoamylase levels (age >3 years)

Low levels of fecal elastase

Supportive features:

Pancreatic lipomatosis

Elevated 72-hour fecal fat excretion and absence of intestinal pathologic condition

Category II

Hypoproductive cytopenias

Neutropenia (absolute neutrophil count <1500)

Anemia or idiopathic macrocytosis

Thrombocytopenia (<150,000)

Bone marrow examination with any of the following:

Myelodysplasia

Leukemia

Myelodysplasia syndrome

Hypocellularity for age

Cytogenetic abnormalities

Supporting features

First-degree or second-degree blood relative with Shwachman–Diamond syndrome

Personal history of

Congenital skeletal abnormalities consistent with chondrodysplasia or a congenital thoracic dystrophy

Height 3% or less, of unclear cause

Deficiency in 2 or more fat-soluble vitamins (A, 25-OHD, and E).

KEY POINTS

- Many exciting advances in our understanding of SDS have occurred in the past few years.
- Our understanding of the natural history and spectrum of disease, diagnosis, and therapy remain limited.
- Ongoing basic and clinical investigations on larger numbers of patients are crucial to better tie together our evolving comprehension of molecular function and clinical manifestations of this multiorgan disease to affect the treatment of patients with this rare disorder.

Table 1

Clinical evaluations for patients with Shwachman-Diamond syndrome

	Interval
Hematology	
CBC	Diagnosis, every 3–6 mo or as clinically indicated
Bone marrow aspirate and biopsy	Diagnosis, every 1–3 y or as clinically indicated
Fe, folate, B_{12} levels	Diagnosis, as clinically indicated
IgG, IgA, IgM levels	Diagnosis, as clinically indicated
HLA testing	As clinically indicated
Gastroenterology	
Pancreatic enzymes (trypsinogen, pancreatic isoamylase, 72-h fat excretion, elastase)	Diagnosis, as clinically indicated
Fat-soluble vitamins (A, D, E)	Diagnosis, 1 mo after initiation of pancreatic enzyme therapy; then every 6–12 mo
Prothrombin time (surrogate for vitamin K)	Diagnosis, 1 mo after initiation of pancreatic enzyme therapy; then every 6–12 mo
Liver panel	Diagnosis, as clinically indicated
Pancreatic imaging (ultrasonography)	Diagnosis
Growth/Skeletal	
Height, weight, head circumference	Yearly
Skeletal evaluation	Diagnosis, as clinically indicated
Densitometry	As clinically indicated, screen in adults
Neurodevelopmental	
Developmental/neuropsychological screening	Diagnosis and regular assessment at followup for school-aged children aged 6–8 y, 11–13 y, and 15–17 y

Abbreviation: CBC, complete blood cell count.