Genetic and clinical characteristics of patients with Shwachman Diamond syndrome with special consideration of treatment with granulocyte-colony stimulating factor

Shwachman Diamond syndrome (SDS) is a rare disorder characterized by exocrine pancreatic insufficiency, bone marrow failure (BMF), congenital abnormalities including the skeleton, and a varying degree of neurodevelopmental delay.[1-3] Patients have a predisposition for myeloid malignancies (myelodysplastic syndrome [MDS] and acute myeloid leukemia [AML]).[4,5]

In the majority of SDS patients (>90%), biallelic germline mutations in the *SBDS* gene can be detected.[6] The clinical manifestation of the disease is extremely variable despite the fact that the majority of patients harbor the same compound heterozygous mutations with the common *SBDS* variants c.258+2T>C and c.183_184 TA>CT.[2,7,8] The most common hematologic finding in SDS patients is from mild to severe neutropenia.[9] Recent studies have shown a positive correlation of hemoglobulin levels, and a negative correlation of leukocyte, neutrophil and platelet counts, with age.[10]

Shwachman Diamond syndrome patients have an increased risk for secondary hematologic malignancies, especially MDS or AML, requiring hematopoietic cell transplantation (HCT). The outcome of myeloid malignancies, even after HCT, remains poor.[10-12]

Therapy with granulocyte-colony stimulating factor (G-CSF) has always been controversial, mainly due to the unproven fear that G-CSF may induce leukemia in SDS patients.

In this retrospective analysis, we report on the clinical/hematologic presentation of SDS patients, as well as hematologic complications in the long-term follow-up, with a special focus on G-CSF therapy.

Between 1994 and December 2022, 121 patients with SDS in Europe were enrolled into the Severe Chronic Neutropenia International Registry (SCNIR); all patients gave written informed consent. After review, data on registration and annual follow-up were entered into a standardized database. In addition, 55 SDS patients from the Russian registry gave written consent to share data with the SCNIR and were included in this analysis. The study was conducted in accordance with the Declaration of Helsinki, under the auspices of the Human Subjects Committee of the Medical School in Hannover and the University Hospital Tuebingen, Germany, and other participating institutions.

A total of 176 patients (91 males, 85 females) from 165 families with a clinical diagnosis of SDS have been included in this study. Median age at clinical diagnosis was 1.75 years (range, 0-23.62 years) and at last follow-up, 9.59 years (range, 0.95-45.58 years), adding up to a total of 2,097 patient years. Twenty percent of patients have reached adulthood (>18 years). At the time of writing, 142 patients were alive, 11 patients were deceased, and 23 patients had been lost to follow-up.

Pathogenic variants in the *SBDS* gene were detected in 99% of the 159 patients tested, revealing the common compound heterozygous variant c.258+2T>C plus c.183_184 TA>CT in 65% of patients. Three percent of patients had monoallelic pathogenic variants but a SDS phenotype which distinguished them from healthy heterozygous *SDBS* carriers. Ten percent of patients had no genetic testing but met the clinical criteria (mainly exocrine pancreatic insufficiency and neutropenia) for SDS (Figure 1).

Neutropenia (in 84% of patients) and exocrine pancreatic insufficiency (in 62%), diagnosed by decreased fecal elastase, were the most common anomalies. The most common clinical co-morbidities involved the endocrine system (Table 1).

Follow-up complete blood count (CBC) and complete information on G-CSF therapy were only available in the SCNIR cohort. Initial CBC (N=108) at a median age of 1.45 years (range, 0-37.85 years) showed neutropenia in 81% of patients, 35% of whom had severe neutropenia (absolute neutrophil count [ANC] <500/μL). Bi-cytopenia was present in 25% of patients, mainly neutropenia plus anemia. Seventeen percent of patients had close to normal blood counts.

In all, 1,423 CBC from 72 patients (excluding patients with MDS / leukemia / pancytopenia / G-CSF / HCT) were analyzed for association between blood counts and age. White blood cell count (WBC) and platelet counts were negatively associated with age, whereas there was a positive association between age and hemoglobulin level and mean corpuscular volume. The decrease in WBC was mainly due to a decrease in lymphocytes, while the median ANC remained stable above 800/μL, with a slight increase to >1,000/μL in adult patients.

Bone marrow (BM) morphology reports were available in 98 patients. MDS was defined according to WHO classification by the treating physician. Blast count of approximately 30% in the BM discriminates between MDS and AML. The first reported BM evaluation was performed at a median age of 3.59 years (range, 0.00-44.61 years), showing hypocel-

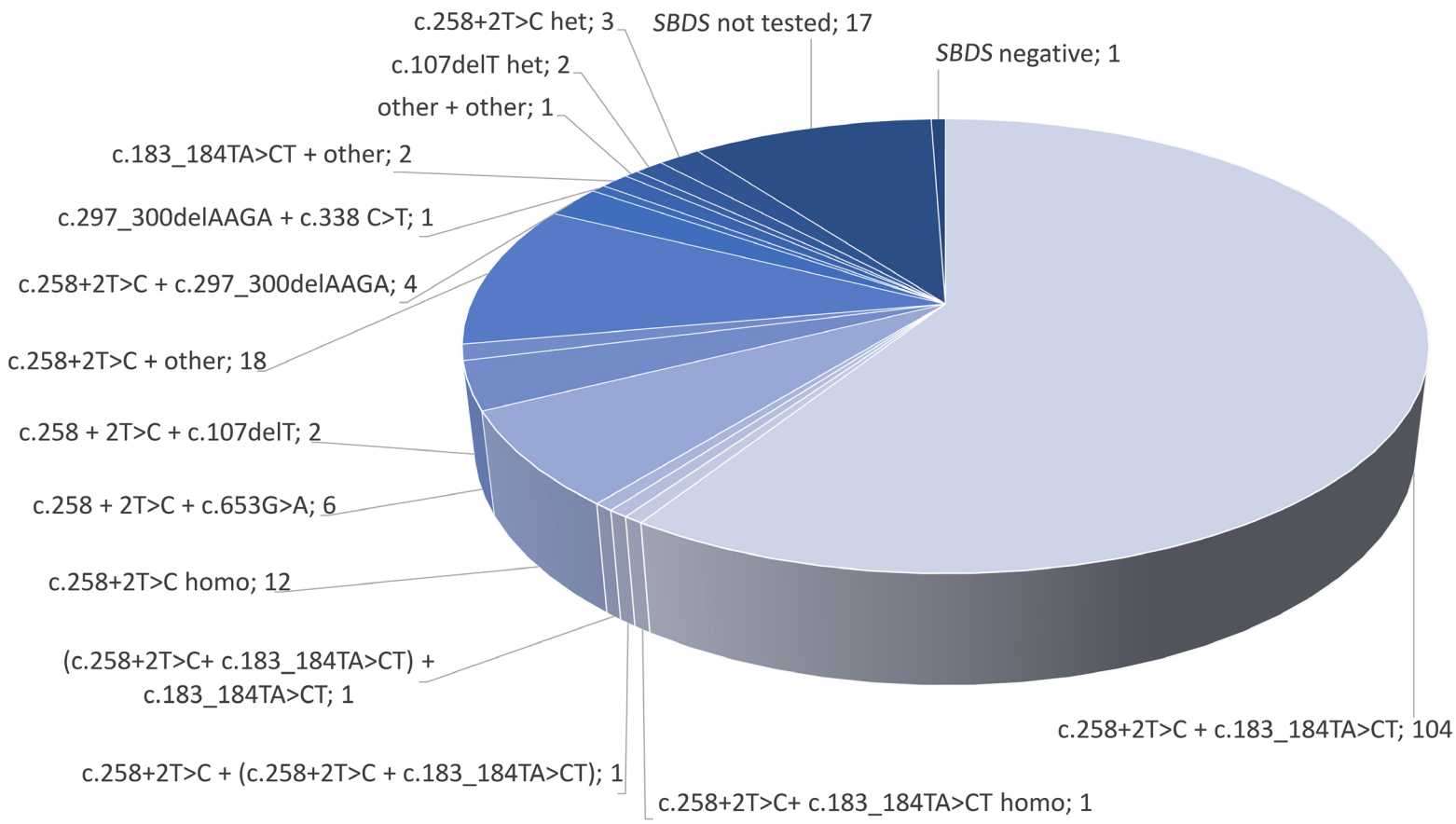

Figure 1. Distribution of *SBDS* gene mutations. *SBDS* gene mutations were detected in 99% of Shwachman Diamond syndrome (SDS) patients tested. Of the 158 patients with mutations, 96% harbored the common c.258+2T>C variant.

lularity in 47%. Left-shifted granulopoiesis was the most common finding (N=23). Maturation arrest was reported in 4 patients and MDS/AML in 4 patients.

The first reported cytogenetic analyses were performed in 97 patients at a median age of 4.73 years (range, 0.22- 44.59 years), detecting abnormalities in 11%: isochromosome 7 (N=3), isochromosome X (N=1), monosomy 7/deletion 20q (N=1), structural abnormalities of chromosome 7p (N=1), incomplete monosomy 7/ trisomy 8 (N=1), deletion 14 (N=1), and complex karyotype (N=3).

Thirty-two percent of patients (N=39) had received G-CSF at some time in their lives. Twenty-five patients received long-term therapy (>1 year) at a median age of 2.48 years (range, 0.05-21.97 years), with a median dose of 2.03 μg/kg/day (range, 0.32-5.0) and a median treatment duration of 2.87 years (range, 2.68-13.58 years) (Figure 2).

All patients responded well to G-CSF therapy, with median ANC increasing to 1,394/μL. Remarkably, no non-responders to G-CSF have been reported, and no patient developed somatic *CSF3R* mutations.

Ten of 121 patients (3 female and 7 male) developed secondary MDS (N=4), AML (N=5), acute lymphoblastic leukemia (N=1) at a median age of 13.77 years (range, 5.12-44.59 years). BM cytogenetic studies were normal in 3, unknown in one, and abnormal in 6 patients with complex aberrant karyotype (N=3), monosomy 7 (N=2, one of 2 with additional deletion 20q) or incomplete monosomy 7 / trisomy 8 (N=1). Two of 6 patients with abnormal cytogenetic studies survived (incomplete monosomy 7 / trisomy 8 [N=1]; complex karyotype [N=1]). Eight patients underwent HCT and 5 are alive with a median follow-up time of 5.07 years (range, 1.11-21.58 years) after HCT. Two patients treated with anti-leukemic chemotherapy only (without HCT) have died.

At the time of MDS/AML diagnosis, 2 of 10 patients were receiving long-term G-CSF therapy (2.03 μg/kg/day and 4.30 μg/kg/day). Another patient had received G-CSF for 17 months 13 years prior to MDS/AML diagnosis. Seven patients have never received G-CSF.

In the total cohort of 176 patients, 11 patients have died at a median age of 14.45 years (range, 0.95-45.57 years; age at death unknown [N=1]) (*Online Supplementary Figure S1*). Causes of death included leukemia (N=2), transplant-related mortality (N=5), leukemia relapse after HCT (N=2), and infections (N=2, RSV-infection and unknown infection). Two successful pregnancies have been reported from two 25-year-old mothers with SDS.

In this study, we evaluated the genotype and clinical / hematologic phenotype at initial enrollment, as well as the natural course of CBC and co-morbidities over time in a large series of SDS patients. Although international guidelines for diagnosis and management exist,[3] not all recommended studies (e.g., X-rays, BM aspirations, surveillance CBC every 3 months) have been performed in every patient. These studies were not mandatory for registry enrollment. Therefore, the incidence of congenital anomalies might be higher than reported. Exocrine pancreatic insufficiency, neutropenia, and skeletal abnormalities were the most common findings at registration. In 176 patients, we observed a wide variability in the clinical phenotype,

with the majority of patients harboring the most common biallelic variants, c.258 + 2T > C and c.183_184TA > CT, but no clear genotype-phenotype correlation. Our data are consistent with observations published by the North American SDS Registry[2,7] and described in other cohort studies.[8,13-15]

Neutropenia was observed in 81% of initially reported CBC, while severe neutropenia was reported in only 35%, and normal blood counts in 17%. BM was hypocellular in the majority of patients.

To understand the natural history of blood counts in SDS patients, we analyzed over 1,400 CBC from 72 patients (excluding patients with G-CSF, BMF/MDS/leukemia). Consistent with the US data,[10] we confirmed that WBC and platelet count were negatively, and hemoglobin level and MCV were positively associated with increasing age. We have shown for the first time that lymphocyte counts are negatively associated with age. The decrease in WBC is mainly due to the decrease in lymphocytes. Still, the median ANC is above 500/μL and the median lymphocyte count above 1,000/μL.

Granulocyte-colony stimulating factor therapy in SDS patients has always been controversial because of the unproven fear of inducing leukemia. Data on the use of

Table 1. Congenital anomalies and clinical comorbidities detected in 176 Shwachman Diamond syndrome patients.

Congenital anomalies	N (%)
Neutropenia	129 (84)
Exocrine pancreatic insufficiency	109 (62)
Musculoskeletal	38 (22)
Patients with >1 skeletal anomaly	9
Thoracic dystrophy/rib anomaly	22
Metaphyseal chondrodysplasia	5
Hip dysplasia	5
Scoliosis	4
Short limbs	3
Clindactyly	1
Osteogenesis imperfecta	1
Clubfoot	1
Knee/foot anomalies	3/1
Unclassified	1
Cardiovascular	11 (6)
ASD/VSD/VSD+ASD	1/1/2
Persistent foramen ovale	3
Aortic isthmus stenosis	1
Sinus node dysfunction	1
Aplasia of inferior vena cava	1
Trabeculae	1
Neurological	4 (2)
Microcephaly	4
Genitourinary	5 (3)
Single kidney	1
Pyelectasis	1
Frehley syndrome	1
Hypospadias	1
Cryptorchidism	1
Other organs	3 (2)
Pulmonary hypoplasia	1
Gallbladder aplasia	1
Pancreatic hypoplasia	1
Ears, nose and throat	7 (4)
Subglottic stenosis	1
Auricular dysplasia	1
Cleft palate	5

Medical comorbidities	N (%)
Endocrine	46 (26)
Diabetes mellitus	5
Hypothyroidism	3
Hypoparathyroidism	1
Hypergonatropic hypogonadism	1
Short stature	17
Bone age delay	19
Skin	44 (25)
Eczema/atopic dermatitis	41
Ichthyosis + dermatitis	2
Vitiligo + dermatitis	1
Liver	24 (14)
Elevated liver enzymes	7
Liver fibrosis	2
Liver cirrhosis	1
Inflammatory liver disease	1
Chronic hepatitis	13
Psychiatric	11 (6)
Autism/autism spectrum disorder	3
Major depressive disorder	1
Schizophrenia	1
Narcolepsy	1
Attention deficit/hyperactivity disorder	2
Behavioral disorders	2
Obsessive compulsive disorder/tics	1
Other	7 (4)
Celiac disease	1
Cystic fibrosis	1
Immune disorder	5
Neurological	2 (1)
Epilepsy/seizures	2
Cancer/benign tumor	2 (1)
Testicular cancer	1
Ossifying fibroma	1

Most common anomalies were neutropenia and exocrine pancreatic insufficiency, followed by skeletal anomalies. Skeletal anomalies were reported by the treating physicians in 22% of patients. Screening X-rays are not mandatory for registry enrollment and not performed routinely by the treating physicians. Therefore, skeletal anomalies are likely under-represented. The most common clinical co-morbidities involved the endocrine system. ASD: atrial septal defect; VSD: ventricular septal defect.

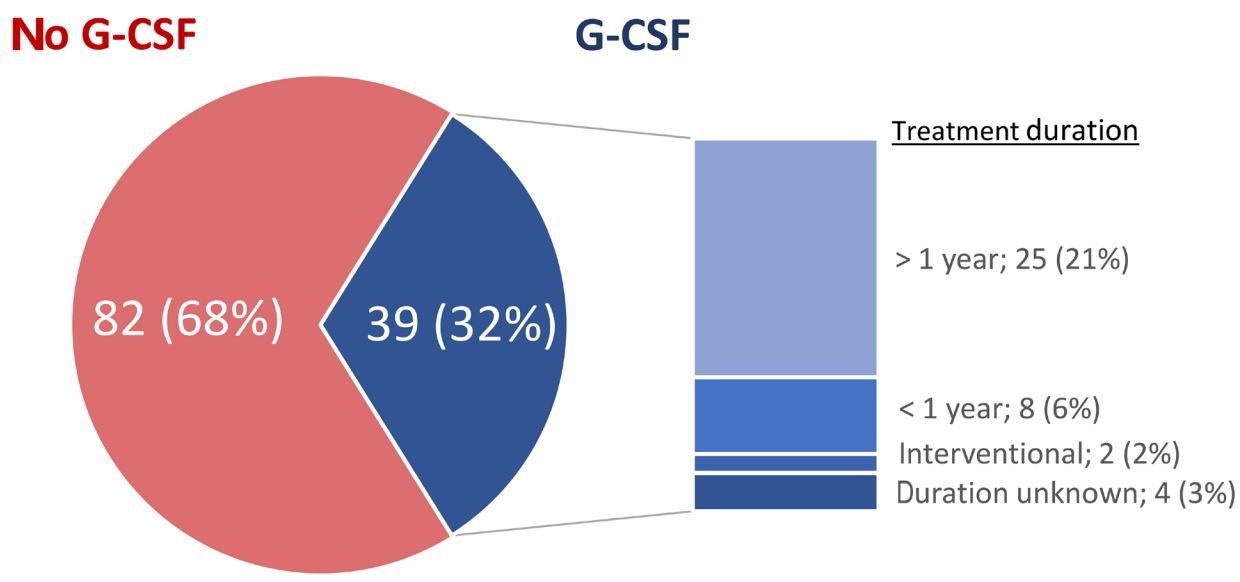

Figure 2. Granulocyte-colony stimulating factor therapy in Shwachman Diamond syndrome patients. Granulocyte-colony stimulating factor (G-CSF) was given only to 32% of patients, despite more patients being neutropenic. 21% of patients were on long-term G-CSF therapy for over one year.

G-CSF in SDS patients are limited. We were able to show that low doses of G-CSF resulted in sufficient ANC. No non-responders to G-CSF were reported. In the SCNIR cohort of 121 SDS patients, 7 of the 10 patients who developed MDS/AML had never received G-CSF. One patient was treated for 17 months but G-CSF was discontinued 13 years prior to MDS/AML. Only 2 patients with MDS/leukemia were receiving G-CSF therapy at the time of MDS/leukemia diagnosis. This emphasizes the fact that the risk of MDS/leukemia in SDS patients is related to the genetic origin of the disorder, as in many other genetic BM failure syndromes.

In conclusion, our current study has shown that despite genetic homogeneity there are variable clinical and hematologic phenotypes in SDS patients. There is an increasing risk of BM failure with age. G-CSF therapy does not increase the risk of developing MDS/leukemia and is, therefore, safe to use in SDS patients with severe neutropenia.

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https://doi.org/10.3324/haematol.2024.286119

Received: June 27, 2024.
Accepted: March 26, 2025.
Early view: March 27, 2025.

Disclosures

No conflicts of interest to disclose.

Contributions

SMH analyzed the data and wrote the manuscript. JS, KW and CZ supervised the study and wrote the manuscript. NG performed the primary data retrieval and summary. ED, IT, SK, MKD, PF, MaS, MiS, YC, TM, LW, GED, HCE, OS, AS and CZ provided clinical data.

Acknowledgments
Thanks to all patients for their consent to participate and our colleagues for data collection.

Funding
This study was supported by grants from the COST-Initiative EuNet-Innochron, the National Institute of Health (NIH; 5 R24 AI 049393-15), the Bundesministerium fuer Bildung und Forschung (BMBF) My Pred, and the José Carreras Leukemia Foundation.

Data-sharing statement
All data are available on request from the corresponding author.

References

1. Shwachman H, Diamond LK, Oski FA, Khaw KT. The syndrome of pancreatic insufficiency and bone marrow dysfunction. J Pediatr. 1964;65:645-663.
2. Myers KC, Bolyard AA, Otto B, et al. Variable clinical presentation of Shwachman-Diamond syndrome: update from the North American Shwachman-Diamond Syndrome Registry. J Pediatr. 2014;164(4):866-870.
3. 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;1242:40-55.
4. Maserati E, Pressato B, Valli R, et al. The route to development of myelodysplastic syndrome / acute myeloid leukaemia in Shwachman-Diamond syndrome: the role of ageing, karyotype instability, and acquired chromosome anomalies. Br J Haematol. 2009;145(2):190-197.
5. Myers KC, Furutani E, Weller E, et al. Clinical features and outcomes of patients with Shwachman-Diamond syndrome and myelodysplastic syndrome or acute myeloid leukaemia: a multicentre, retrospective, cohort study. Lancet Haematol. 2020;7(3):e238-e246.
6. Boocock GR, Morrison JA, Popovic M, et al. Mutations in SBDS are associated with Shwachman-Diamond syndrome. Nat Genet. 2003;33(1):97-101.
7. Burroughs L, Woolfrey A, Shimamura A. Shwachman-Diamond syndrome: a review of the clinical presentation, molecular pathogenesis, diagnosis, and treatment. Hematol Oncol Clin North Am. 2009;23(2):233-248.
8. Thompson AS, Giri N, Gianferante DM, et al. Shwachman Diamond syndrome: narrow genotypic spectrum and variable clinical features. Pediatr Res. 2022;92(6):1671-1680.
9. Cesaro S, Pegoraro A, Sainati L, et al. A prospective study of hematologic complications and long-term survival of Italian patients affected by Shwachman-Diamond syndrome. J Pediatr. 2020;219:196-201.e1.
10. Furutani E, Liu S, Galvin A, et al. Hematologic complications with age in Shwachman-Diamond syndrome. Blood Adv. 2022 11;6(1):297-306.
11. Donadieu J, Michel G, Merlin E, et al. Hematopoietic stem cell transplantation for Shwachman-Diamond syndrome: experience of the French neutropenia registry. Bone Marrow Transplant. 2005;36(9):787-792.
12. Myers K, Hebert K, Antin J, et al. Hematopoietic stem cell transplantation for Shwachman-Diamond syndrome. Biol Blood Marrow Transplant. 2020;26(8):1446-1451.
13. Kuijpers TW, Alders M, Tool AT, Mellink C, Roos D, Hennekam RC. Hematologic abnormalities in Shwachman Diamond syndrome: lack of genotype-phenotype relationship. Blood. 2005;106(1):356-361.
14. Delaporta P, Sofocleous C, Economou M, Makis A, Kostaridou S, Kattamis A. The Greek Registry of Shwachman Diamond-Syndrome: molecular and clinical data. Pediatr Blood Cancer. 2017;64(11):1-4.
15. Ikuse T, Kudo T, Arai K, et al. Shwachman-Diamond syndrome: nationwide survey and systematic review in Japan. Pediatr Int. 2018;60(8):719-726.