⊛ **Thieme**

Shwachman-Diamond Syndrome and Diabetes: An Update from the Italian Registry and Review of the Literature

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ABSTRACT

The issue of a possible association between Shwachman-Diamond Syndrome and diabetes has been debated for many years. This review updates the Italian Shwachman-Diamond registry, confirming our previous findings that suggest that these patients might be at higher risk of developing diabetes, particularly type 1. These data are of relevance in the clinical follow-up of patients in everyday life, emphasizing the need for early diagnosis and timely intervention.

Introduction

Shwachman-Diamond syndrome (SDS; OMIM 260400) is a rare autosomal recessive disorder with a prevalence in Italy of 1/168000 [1]. The condition is characterized by the association of exocrine pancreatic insufficiency and bone marrow dysfunction with specific chromosomal abnormalities [2], skeletal abnormalities [3], and recurrent infections related to neutropenia and immune dysfunction [4]. The diagnosis is based on the recognition of a typical clinical picture, followed by the presence of biallelic pathogenic mutations in the Shwachman-Bodian-Diamond Syndrome (*SBDS)* gene. In most cases, two common mutations, [c.258 + 2T > C] and [c.183_184delTAinsCT], resulting from gene conversion, are identified [5], while in a minority of cases uncommon mutations are observed [6]. Recently, genetic heterogeneity was demonstrated in a few cases with SDS or SDS-like phenotypes with pathogenic mutation in different genes, such as *DNAJC21, EFL1*, and *SRP54* [7–9]. Diabetes as a possible frequent comorbidity of SDS has been debated extensively, mostly as anecdotical reports; our group included data from the Italian registry (RI-SDS) and reported a review in 2011 [10].

Material and methods

Statistical analysis

The cumulative incidence of diabetes was computed using the cumulative incidence method, where the occurrence of diabetes was the event of interest, whilst death due to any cause was considered a competing event. Data were analyzed irrespective of age, with the time of observation was since birth, so that the time of the event was the same as the age at which the event was identified in the patient.

The analysis was performed using the statistical software SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Results

We reviewed data available from the literature about co-occurrence of diabetes (any type) and SDS and updated information from the Italian registry, which, as of February 2024, included 145 cases.

▶ **Table 1** presents the cases published prior to the identification of the *SBDS* gene [11–16]. Parents of the newborn reported by Filippi et al. [16] requested our group to perform a prenatal diagnosis in their subsequent pregnancy; however, a biological sample of the newborn clinically diagnosed as SDS failed to show any mutation in the *SBDS* gene and prenatal diagnosis was thus not performed.

Six patients were reported to be affected with diabetes; however, considering only a series of cases and the number of patients with documented abnormal glucose tests, 4 cases out of 122 (ref.11 n = 4; ref.13 n = 5; ref. 14 n = 25; ref. 15 n = 88) were affected by diabetes or had an abnormal Glucose Tolerance Test (GTT) [17] (3,2 %).

▶ **Table 2** includes patients (mostly case reports) with proven *SBDS* mutations [18–26]. In two case series [22, 23], the incidence of diabetes was, respectively, 4 % (1/25) and 5.2 % (1/19) (mean 4.5 %). ▶ **Table 3** presents updated records from the Italian Registry of SDS patients, indicating published cases [10, 27]; UPN refers to cases reported by our group. Both types 1 and 2 of diabetes were reported: 9/145 patients developed diabetes (6.2 %), with 5 cases with type 1 diabetes (3.4 %) and 4 cases with type 2 diabetes (2.7 %).

BMI in these 9 SDS diabetic patients was 21.1 ± 6.6, compared to 19.9 ± 5.4 in 124 non-diabetic SDS cases. BMI in UPN54 (diabetes type 2, positive family history, ▶ **Table 3**) was 34.4 – classifying as obesity class 1, while in UPN86 (diabetes type 1, no family history, ▶ **Table 3**) it was 29.1– indicating overweight status.

▶ **Fig. 1** presents the cumulative incidence of diabetes (all types) relative to 9 cases among 145 patients included in the RI-SDS only. This figure shows a 30-year cumulative incidence of diabetes of 8.9 % (95 % C.I. 3.3–18.0).

Cumulative data from the literature, as well as RI-SDS, indicated that type 1 diabetes was reported more frequently, with 13 cases, while type 2 was reported in 5 (▶ **Table 2, 3**). Males and females were similarly affected (8M/8F, sex not reported in one case).

Discussion and conclusions

In preparing this review we decided to gather all the defined diagnoses of diabetes (and abnormal GTT), as, based on the available literature data, it was not possible to define really homogeneous groups for each type of disease, and some cases do not perfectly fit the description of different types of diabetes. Our main goal should have been to try to assess whether patients affected by SDS were indeed at a higher risk for poor glucose control, as it would be clinically relevant in their management.

In cases diagnosed as SDS based solely on clinical signs, as the disease-causing gene has not yet been identified (▶ **Table 1**), observations about the presence of diabetes or at least GTT are anecdotical, with very few details. However, they show that comorbidity of diabetes and SDS has been noticed shortly after the description of the disease.

As shown in ▶ **Table 2**, SDS cases in which the clinical diagnosis was confirmed by genetic analysis, the case described by Akdogan et al., [21] was listed because it fits the diagnosis of SDS, although the genetic test reported "monosomy 7" is by no means a valid indicator for genetically validating the diagnosis of SDS.

Myers et al., 2013 [22] reported significant differences between patients with *SBDS* and the general population also when abnormal GTT are considered, even if a formal diagnosis of diabetes is not reached.

Notably, the incidence percentages of types 1 or 2 diabetes and abnormal GTT were comparable within the two groups for which more available data: SDS with a confirmatory genetic test at 4.5 % and RI-SDS at 6.2 %.

The ages at which various types of diabetes were diagnosed varied greatly, from childhood to adulthood (▶ **Table 1–3**), and did not correlate with mutation type (as expected) nor with type of diabetes.

▶ **Table 1** Cases published prior to identification of the *SBDS* gene as a disease-causing gene of SDS.

Reference	No. of cases with diabetes/sex/(total number of cases)	SDS diagnosis	Diabetes type	Diabetes age onset, yrs	Family history
Shmerling et al., 1969	1/?/ (4)	Clinical	Unspecified	7	Yes (brother, maternal aunt, and sister with abnormal GTT)
Shwachman and Holsclaw, 1972	1/? /abnormal GTT	Clinical	Unspecified	nr	nr
Aggett et al., 1980	1/? /abnormal GTT (5 tested, 21 studied)	Clinical	Unspecified, abnormal GGT	nr	nr
Mack et al., 1996	1/?/ (25)	Clinical	Unspecified; insulin-dependent	adolescence	nr
Ginzberg et al., 1999	1/?/ (88)	Clinical	NIDDM	nr	nr
Filippi et al., 2002	1/F preterm newborn	Clinical	Neonatal transient DM, 1st day of life, insulin infusion	neonatal	Yes (mother affected with IDDM)
M: male; F: female; DM: diabetes mellitus; NIDDM: non-insulin-dependent diabetes mellitus; IDDM: insulin-dependent diabetes mellitus; GTT: glucose tolerance test; nr: not reported.					

▶ **Table 2** Cases published after identification of the *SBDS* gene as a disease-causing gene of SDS.

Reference	No. of cases with diabetes/sex/ (total number)	SDS clinical diagnosis	*SBDS* genotype	Diabetes type	Diabetes age of onset	Family history
Rosendhal et al., 2005	1 /M	At 6 yrs: short stature, fatty stools	c.95A>G /c.258+2T>C	Type 1	26 yrs	nr*
Kamoda et al., 2006	1 /F	As a neonate: neutropenia, bone marrow failure	c.183_184delinsTA>CT/c.258+2T>C	GTT with diabetic pattern	15 months	nr
Kawashima et al., 2006	1/ F/ (2)	Infancy: cyclic neutropenia, short stature, narrow chest, soft stool	c.183_184delinsTA>CT/ c.258+2T>C	IDDM	5 yrs	nr
Akdogan et al., 2011	1/F	29 yrs: low serum amylase/lipase, neutropenia	Genetic test? ^	Acute diabetic ketoacidosis	29 yrs	nr
Myers et al., 2013	1/?/ (25)	No details	Genetic test performed but not reported in detail	Type 1	nr	Yes, type 1
Bogusz-Wójcik et al., 2021	1/M/ (19)	Diagnostic criteria for SDS as in Dror et al., 2011	Genetic test performed but not reported in detail	Type 1	nr	nr
Miguélez González M et al., 2021	1/F	Short stature, metaphyseal chondrodysplasia	Genetic test performed but not reported in detail	Type 1	41 yrs	nr
Navasardyan et al., 2023	1/F	<1yr	c.183_184delinsTA>CT/c.523C>T	Type 1	1.8 yrs	nr

IDDM: insulin-dependent diabetes mellitus; GTT: glucose tolerance test; na: not available; *according to his parents, his sister died at 6 months of age, with a similar phenotype. ^ it is inappropriate to quote monosomy 7 as a genetic cause of SDS, as reported in the paper.

▶ **Table 3** Cases registered in the Italian registry as at October 2023.

| UPN/SEX	*SBDS* genotype	DM type/therapy	DM age onset	Family history
UPN 23[a]/F	c.258+2T>C/c.183_184delinsTA>CT	DM type 1/insulin	4 years old	No
UPN 39/M	c.258+2T>C/c.183_184delinsTA>CT	DM type 2/diet and glycemia monitoring	41 years old	Yes*
UPN 40/F	c.258+2T>C/c.183_184delinsTA>CT	DM type 2/diet and glycemia monitoring	15 years old	No
UPN 45[b]/M	c.258+2T>C/c.183_184delinsTA>CT	DM type 1/insulin	2 years old	No
UPN 47/M	c.258+2T>C/c.183_184delinsTA>CT	DM type 2/diet and glycemia monitoring	14 years old	nr
UPN 54/F	c.258+2T>C/c.183_184delinsTA>CT	DM type 2/diet and glycemia monitoring	9 years old	Yes**
UPN 86/M	c.258+2T>C/c.183_184delinsTA>CT	DM type 1/insulin	33 years old	No
UPN 107/M	c.258+2T>C/c.258+2T>C	DM type 1/insulin	29 years old	No
UPN 110[c]/ M	c.258+2T>C/c.183_184delinsTA>CT	DM type 1/insulin	13 years old	No

UPN: unique patient number; DM: diabetes mellitus; IDDM: insulin-dependent diabetes mellitus; GTT: glucose tolerance test; no: no family history; (*): Mother developed DM type 2 when 50 yrs; (**) father developed DM type 2, age unknown; ([a]) Patient 1 in ref [10]; ([b]) Patient 2 in ref [10]; ([c]) Patient described in ref [27].

An autoimmune reaction is commonly accepted to play a relevant role in the pathogenesis of type 1 diabetes. SDS patients may present abnormalities in immune regulation (reduction in circulating B, T cells, and natural killer cells, as well as low immunoglobulin levels [3, 28]), which in turn may play a role in the development of autoimmune disorders, including type 1 diabetes [10].

The etiology of type 2 diabetes relates to the development of resistance to insulin in muscular, adipose, and liver cells, which lim-

its their ability to take up the appropriate amount of glucose, at the same time, the pancreas is unable to produce enough insulin. It is conceivable that general exocrine insufficiency, often associated with pancreatic atrophy, may also impact endocrine function for SDS.

Likewise, cystic fibrosis-related diabetes (CFRD), clinically different from both type 1 and type 2 diabetes, is well known, with an
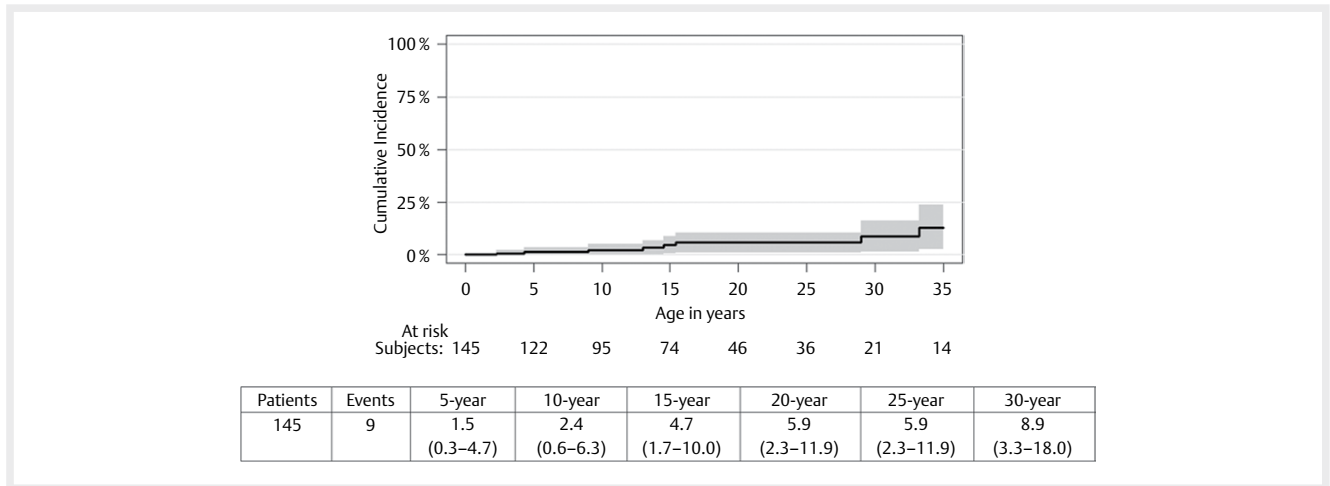
▶ Fig. 1 Cumulative incidence of diabetes in 145 patients with Shwachman-Diamond Syndrome (SDS) from the Italian Registry.

Patients	Events	5-year	10-year	15-year	20-year	25-year	30-year
145	9	1.5 (0.3–4.7)	2.4 (0.6–6.3)	4.7 (1.7–10.0)	5.9 (2.3–11.9)	5.9 (2.3–11.9)	8.9 (3.3–18.0)

age-dependent prevalence ranging from 20 % in adolescents to 50 % in adults [29].

Data pertaining to the prevalence of type 1/2 diabetes in general populations vary greatly with time and country [30]. Recent information released by the Italian Health Ministry (https://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?menu=notizie&id=5900) reports a prevalence of 0.5 % for type 1 diabetes and 6 % for type 2 diabetes.

Among cases entered in the RI-SDS, which likely includes almost all SDS cases in Italy, the prevalence of type 1 diabetes was clearly higher than expected (3.4 % vs 0.5 %) as previously reported [10]. The prevalence of RI-SDS type 2 might be comparable to what is observed in the general population; however, while type 2 diabetes typically develops after age 45, in three out of four cases in the RI-SDS, the age of onset is much younger (9, 14, and 15 years).

We purposely did not attempt to perform extended statistical analysis of the data because of their heterogeneity, differences in reporting, and regional incidence differences when Italian data are considered. Given that data from RI-SDS are reasonably homogeneous for diagnostic procedures, we estimated the cumulative incidence of diabetes, any type, and its age incidence for the Italian population; again, data of both type 1 and 2 were analyzed together, as the primary aim of this report was to assess the relevance of abnormal glucose control in SDS patients.

Diabetes of any type, as a comorbidity of SDS, has been reported many times (▶ **Table 1–3**).

Even though many of the published papers on this topic are case reports, with the risk of overestimating the prevalence, the occurrence of the same observation in some series of cases as well as in the Italian registry suggests that it is not just an anecdotical observation. The high prevalence of "atypical diabetes" in another disease with exocrine pancreatic insufficiency, such as cystic fibrosis, supports this observation.

One limitation of the paper is the scarcity of clinical data from the literature on diabetes in patients with SDS, and the forms used to collect data in the RI-SDS do not contain specific questions about diabetes as it is not yet recognized as one of the main comorbidities in this patient population.

We suggest the following actions: i) routine control of glycemic status should be included in the disease specific clinical tests for SDS early in life, given the age at which some cases of type 2 diabetes are diagnosed, ii) reporting new cases of diabetes in SDS patients is worthwhile to better describe clinical differences, if any, with typical forms, and iii) a concerted international effort is necessary to assess its prevalence in many different registries, which will define the relevance of diabetes in the natural history of SDS.

The data we collected are of relevance in the general clinical follow-up of SDS patients in everyday life for early diagnosis and early treatment of abnormal glucose metabolism.

Acknowledgement

Conflict of Interest

The authors declare that they have no conflict of interest.

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