REVIEW

Shwachman–Diamond syndrome: UK perspective

G W Hall, P Dale, J A Dodge

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So much has been added to our knowledge of Shwachman–Diamond syndrome (SDS) since it was last reviewed in this journal some 25 years ago,[1] that there is now an urgent need to bring the condition to the attention of a new generation of paediatricians. SDS, although a rare autosomal recessive disorder, demands wide attention because it features in the differential diagnosis of a number of important childhood diseases. It can be diagnosed in children of all ages, or in adults. SDS most commonly presents in infancy with features of exocrine pancreatic insufficiency, bone marrow dysfunction, and short stature.

After cystic fibrosis (CF), SDS is the second most common cause of exocrine pancreatic insufficiency in children, and it must always be considered when patients present with CF-like symptoms. Haematological problems can be varied and intermittent, so the diagnosis is not always immediately obvious. Although neutropenia is the most common presenting haematological feature, there is also a greatly increased risk of developing acute leukaemia later in life. Other organs which can be affected include the skeleton (metaphyseal dysostosis, epiphyseal dysplasia), teeth and oral cavity, liver, heart, kidneys, and skin. In addition, new evidence suggests that affected children may have learning difficulties and impaired psychological development.

Until recently there has been no confirmatory diagnostic test for this condition. The gene responsible for SDS was cloned in 2002[2] and molecular diagnostic testing is now available in the UK.

The purpose of this review is to promote awareness of SDS and its diagnosis and to offer recommendations for multidisciplinary management.

The establishment of a UK registry and database will allow a better understanding of the natural history of the syndrome and contribute to the provision of comprehensive clinical care for patients.

See end of article for authors' affiliations

Correspondence to: Dr G W Hall, Paediatric Haematology/Oncology Unit, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK; georgina.hall@paediatrics.ox.ac.uk

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CLINICAL PRESENTATION

A syndrome associating exocrine pancreatic insufficiency with leucopenia was first described in 1961 by Nezelof and Watchi,[3] and later in 1964 by Shwachman *et al*[4] and Bodian *et al*.[5] When associated skeletal changes were observed by Burke *et al* in 1967[6] and Pringle *et al* in 1968,[7] the syndrome was re-described as a triad of exocrine pancreatic insufficiency, bone marrow failure, and bony changes—predominately metaphyseal dysostosis. Any of the following features should alert clinicians to the possibility of a diagnosis of SDS.

(a) Pancreatic/gastrointestinal

Exocrine pancreatic failure in children is usually due to cystic fibrosis, but SDS is the second most common cause. Pearson's syndrome, Johanssen–Blizzard syndrome, and severe malnutrition are other extremely rare possibilities.

Histological examination of the pancreas reveals a severe paucity of acini with fatty replacement but preserved duct and islet architecture.[8 9] More than 98% of the exocrine acinar capacity of the pancreas must be lost before there are clinical symptoms of pancreatic insufficiency. Steatorrhoea is noted in the first 6 months of life in about 50% of affected infants, and in 90% by the age of 1 year. Clinical symptoms of hypoalbuminaemia are rarely seen. A significant proportion, however, retain adequate digestion (''pancreatic sufficiency'') and, in contrast to cystic fibrosis, pancreatic function often improves with age. Exocrine pancreatic functional abnormality may be demonstrable by subtle abnormalities (for example, deficiency of serum pancreatic isoamylase[10]), even in the minority who do not have overt evidence of malabsorption/maldigestion. If enzyme secretion is measured in pancreatic sufficient patients, it is usually 10–14% of normal.[11]

Excluding cystic fibrosis by sweat test is essential. Seventy two hour faecal fat collection or the simple recognition of excessive fat globules on stool microscopy remain helpful screening tests, but faecal fat measurement is increasingly less available as a laboratory test and other tests such as the steatocrit have not been universally accepted as valid alternatives. The serum immunoreactive trypsin (IRT) may be normal or low in SDS, because in contrast to cystic fibrosis the pancreatic failure is due to hypoplasia, not obstructive/destructive pancreatitis. Screening for pancreatic insufficiency by measuring faecal chymotrypsin may also be unreliable in the presence of diarrhoea, but faecal elastase may be a better screening test although it awaits further evaluation in SDS. Pancreatic stimulation tests are invasive and should only be carried out in specialised units. Pancreatic ultrasonography and CT will often show a small, structurally abnormal pancreas composed mainly of fat.[8 12] There is no evidence of pancreatic endocrine dysfunction in SDS.

The recognition of pancreatic dysfunction has been regarded as an essential part of the diagnosis of SDS, but it remains to be seen whether this rule holds true now that molecular diagnosis is possible. Fat soluble vitamin levels

and vitamin K dependent prothrombin time may be abnormal in untreated pancreatic insufficiency, and should therefore be monitored.

Liver transaminases are raised in 60% of SDS patients. Hepatomegaly is found in around 15%[12] and is probably due to steatosis (''fatty liver''). These abnormalities regress with age and appear to have no long term sequelae.[8]

(b) Haematological

Although the exact incidence is not known, SDS is the third most common congenital bone marrow failure syndrome after Fanconi and Diamond–Blackfan anaemia. Varying degrees of cytopenia, an increased risk of developing myelodysplastic syndrome (MDS), and acute myeloid leukaemia (AML) are the main haematological manifestations of SDS. Haematological features are variable, which often results in a delay in diagnosis. In one family the diagnosis of SDS was only made retrospectively, when two brothers presented, as adults, with AML.[13]

The most common single cytopenia is neutropenia (seen in >80% of patients), which can be persistently or intermittently severe, with neutrophil counts of $<0.5\times10^9$/l.[14] The neutrophils of patients with SDS often exhibit impaired mobility, migration, and chemotaxis, so that severe recurrent infections (otitis media, pneumonia, septicaemia, etc) may be seen in patients without marked neutropenia. Anaemia is the next most common cytopenia and is usually mild and normochromic–normocytic, although it can be macrocytic.[15] Many patients develop a mild, and clinically insignificant thrombocytopenia, as defined by a platelet count of $<150\times10^9$/l. However, marked or significant thrombocytopenia ($<20\times10^9$/l) does occur rarely and is seen in association with the onset of AML. Pancytopenia, including severe aplastic anaemia (SAA), has also been reported. In addition, normal haemopoiesis is probably affected by defects in the marrow–stromal support structure.[15] Like most of the bone marrow failure syndromes there is a predilection for myelodysplasia and malignant transformation. The detection of various, often complex, acquired cytogenetic abnormalities in the bone marrow is a marker of clonal evolution and often heralds transformation to a more severe form of MDS and/or AML.[15] Strikingly, an extremely rare chromosomal abnormality, isochromosome (a mirror image chromosome, with two identical arms on either side of the centromere) i(7)(q10) has been detected in about 25% of SDS patients with MDS.[16] Isochromosome (7)(q10) seems to persist stably in the marrow of certain patients without progression of MDS to AML.[15–18] The incidence of transformation to AML has been reported as 5% in children,[1 15] but increases as patients reach adulthood to approximately 25%.[14]

(c) Growth and skeletal abnormalities

At birth, infants with SDS are on lower growth centiles. Their height-for-weight, however, is normal. The primary skeletal defects are related to abnormal development of growth plates, particularly the metaphyses. All patients exhibit delayed bone age and some show progressive spinal deformitites (kyphosis, scoliosis, and vertebral collapse). Metaphyseal chondrodysplasia occurs in 40–80%[1 8 19] of children with SDS, although it is usually asymptomatic and most often involves the femoral head. These changes can be seen on a plain *x* ray but may not be apparent until after the first year of life. Significant osteoporosis and osteomalacia is often seen, most likely secondary to impaired vitamin D and vitamin K absorption, which results in increased spinal and peripheral fractures.[20]

Approximately 30–50% of patients have thoracic cage defects, including shortened ribs with flared ends and chostochondral thickening.[1 8 19 20] Digit abnormalities (syndactyly, clinodactyly, and supernumerary thumbs) have also been reported. Stature in later life is very variable, but in some, stunting seems to be an intrinsic feature of the syndrome and appears not to be directly related to exocrine pancreatic dysfunction.

(d) Oral/dental

There are significant oral health issues that are often not addressed or appropriately managed, mainly due to lack of awareness. Mucositis and periodontal infections are frequently seen in individuals who are profoundly and persistently neutropenic.[21] However, there is an increased incidence of tooth enamel defects (dental dysplasia) in children with SDS, including hypomaturation, hypocalcification, and hypolasia.[22] Dental caries and tooth surface loss are seen in about a third of patients.

(e) Psychological

It is becoming increasingly apparent that many children with SDS suffer from neurological, learning, and/or behavioural difficulties.[1 23] Recent preliminary studies suggest that a significant number of children experience cognitive and attention difficulties as well as problems with emotional control.[24]

(f) Immune dysfunction

Various defects in lymphocyte populations have been reported, both quantitative (including low IgG levels) and qualitative (including lack of specific antibody production).[25] The clinical significance of these findings is unclear.

(g) Other features

Severe eczema is often seen at presentation. Ichthyosis, cleft palate, renal calculi, and myocardial fibrosis have all been reported in patients with SDS.[26 27]

DIAGNOSIS

When a case of SDS is suspected, the diagnostic criteria in box 1 should help in establishing the diagnosis. The presence of skeletal abnormalities, short stature, and hepatic impairment would support the diagnosis.

Box 1: Diagnostic criteria for SDS (as used by Dror and Freedman)[15]

Exocrine pancreatic dysfunction (at least one of the following):

- Abnormal quantitative pancreatic stimulation test
- Serum cationic trypsinogen below the normal range
- Abnormal 72 hour faecal fat analysis plus evidence of pancreatic lipomatosis by ultrasonographic examination or computerised tomography

AND

Haematological abnormalities (at least one of the following):

- Chronic (on two occasions at least 6 weeks apart) single lineage or multilineage cytopenia with bone marrow findings consistent with a productive defect:
  - Neutrophil $<1.5\times10^9$/l
  - Haemoglobin concentration <2 standard deviations below mean, adjusted for age
  - Thrombocytopenia $<150\times10^9$/l
- Myelodysplastic syndrome

RECENT DEVELOPMENTS

Registry/database

A proposal for an international SDS database has been supported and encouraged by patient groups worldwide. National organisations are setting up their own registries and databases. Dr Elene Psiachou-Leonard in Leicester is awaiting MREC approval for the UK SDS registry (elene.psiachou-leonard@uhl-tr.nhs.uk).

Identification of SBDS gene

In 2002, researchers from Toronto identified the gene that is altered in SDS. The Canadian team studied 250 families,[2] a feat only possible with good international collaboration and organisation. Unlike Fanconi anaemia, which may result from mutations in more than five different genes, and Diamond–Blackfan anaemia (25% of families have mutations in the RPS19 gene), more than 90% of the SDS patients had alterations in one single gene on chromosome 7. The SBDS gene (named after Shwachman–Bodian–Diamond), located on 7q11, is predicted to code for a 250 amino acid protein of (currently) unknown function. The transcript of the normal gene is widely expressed in the pancreas, bone marrow, and leucocytes and assumed to be necessary for the normal development of these tissues.

Molecular basis of SDS

The SBDS gene has an adjacent pseudogene (a non-functional but almost identical gene) on 7q11. In the majority of patients with SDS it appears that during meiotic recombination the two genes, lying close to each other, have ''recombined'' so that parts of the pseudogene are incorporated into the normal SBDS gene. The altered SBDS gene then has non-functional elements from the pseudogene, which renders it dysfunctional. Fourteen such mutations have been identified in the SBDS gene that lead to the SDS phenotype and just two account for 94% of all altered alleles. Currently, little is known about whether certain mutations result in different disease presentations or severity. The construction of molecular and clinical databases should, in due course, allow these relationships to be identified.

MANAGEMENT

Management of children with SDS should be multidisciplinary. The child should be primarily under the care of a local general paediatrician, with long term, regular follow up (see box 2) by a paediatric gastroenterologist and haematologist. The multidisciplinary team (MDT) should also include a dentist, dietician, and psychologist.

Below are recommendations for clinicians caring for children with SDS based on consensus findings from the 3rd International Congress on SDS in June 2005 (Cambridge, UK).

Gastrointestinal

The mainstay of treatment is pancreatic enzyme supplements together with a high calorie diet. The enzyme dose should be regulated according to symptoms, such as steatorrhoea, abdominal pain, and growth parameters. It is essential that a paediatric dietician is involved in the patient's care to ensure that appropriate doses of fat soluble vitamins are prescribed. The requirement for enzyme supplements may decrease with age as previous studies have shown that almost 50% of SDS patients have a near normal fat balance by 4 years of age.[8 9 21]

Haematological

Febrile neutropenia or overt infection is treated with broad spectrum antibiotics. Granulocyte colony stimulating factor (G-CSF) can be used, but is usually reserved for cases of severe life threatening sepsis and rarely as prophylaxis. Blood and platelet transfusions are given as required for anaemia and thrombocytopenia.

Depending on the degree of baseline haematological abnormalities, a full blood count is performed every 3–6 months and more frequently if symptoms require. Annual or biennial surveillance bone marrows are performed to look for the acquisition of cytogenetic abnormalities in the absence of overt changes on the peripheral film. Annual marrows are performed on those requiring regular use of G-CSF as there have been concerns that intensive use of G-CSF may accelerate transformation.

As SDS related leukaemia carries a poor prognosis (17 of 20 patients reported with AML died either because of refractory disease or treatment related toxicity[15]), there is a desire to do something definitive before AML develops. The only attempt at definitive treatment of these haematological problems, largely in those with clonal progression to severe MDS, has been with bone marrow transplantation (BMT).[15 18] However, it is becoming increasingly clear that bone marrow transplantation is not indicated if the only cytogenetic abnormality in the marrow is i(7)(q10).[18] Experience with BMT in SDS patients is limited but overall outcomes are similar to non-SDS patients with MDS/AML or SAA, although SDS patients appear to suffer more toxicity from the procedure.[28]

Abnormalities in other systems

Symptomatic skeletal, dental, or other problems, which may predominate over gastrointestinal and haematological problems in some children, should be dealt with by the appropriate specialist teams, and monitored closely, via the MDT clinic and local lead clinician.

RECOMMENDATIONS

Any child with steatorrhoea and poor weight gain and with CF excluded should be investigated for exocrine pancreatic insufficiency. Universal screening of neonates will identify the majority of new children with CF. Faecal elastase is a good non-invasive test for exocrine pancreatic insufficiency.

Box 2: Minimum requirements for follow up

These should include:

- DNA confirmation of the diagnosis, and offer of screening to siblings where appropriate
- General clinical review and blood count every 3–6 months
- Serum concentrations of vitamin A, 25-OH vitamin D, and vitamin E, and prothrombin time six monthly
- Annual review of steatorrhoea and pancreatic enzyme supplementation
- A surveillance bone marrow, with cytogenetics, performed annually or biennially
- Dental review at least annually, ideally every three months, for preventive treatment, cleaning, and plaque removal. Oral infections must be treated promptly by local measures and antibiotics
- Review of growth, pubertal development, nutrition, and gastrointestinal symptoms at least every six months, with dietetic involvement.
- *x* ray examinations every five years to review the evolution of skeletal abnormalities. If there is evidence of abnormal long bone alignment, referral to an orthopaedic surgeon may be appropriate
- Psychometric assessment at or before school entry, and subsequent educational/psychological help as required

Any child suspected of having SDS needs to be reviewed by a gastroenterologist and a haematologist, and have initial *x* ray investigations, to confirm a clinical diagnosis (see box 1). This can, and should now, be followed by a confirmatory genetic diagnosis.

Natural history (what do you tell the parents)

The projected median survival of patients with SDS has been calculated to be more than 35 years.[29] The development of national registers and an international collaborative database, as agreed at the third International Conference on SDS held in Cambridge in 2005, will help to elucidate those clinical and genetic variations which correlate with better or worse prognosis.

USEFUL CONTACT ADDRESSES

DNA testing in the UK

- Dr Martin J Schwarz, PhD, FRCPath, Consultant Clinical Molecular Geneticist, National Genetics Reference Laboratory, Regional Molecular Genetics Service, St Mary's Hospital, Hathersage Road, Manchester M13 0JH, UK. Tel: 0161 276 6129; fax: 0161 276 6606; email: martin.schwarz@CMMC.nhs.uk.
- Joanna Hinks (Registered Clinical Scientist) at the same address. Tel: 0161 276 3265; email: joanna.hinks@cmmc.nhs.uk.

DNA testing in North America

Information regarding the SDS test in North America can be obtained from www.sickkids.ca/Molecular/MGLHomeSite.ASP.

Family/patient support groups

- Shwachman–Diamond Support UK (SDS UK), the registered UK charity for patients and families: 18 Merevale Avenue, Nuneaton, Warwickshire CV11 5LU, UK. Contact: Sharon Clusker on 02476 345199. Email: enquiries@shwachman-diamondsupport.org. Reg. Charity No: 1081122; www.shwachman-diamondsupport.org.
- Shwachman–Diamond Syndrome International, USA: 5195 Hampstead Village Ctr Way, PMB #162, New Albany, OH 43054, USA. Fax: 614-939-0752; email: 4sskids@shwachman-diamond.org; www.shwachman-diamond.org.
- Website of The Hospital for Sick Children, Toronto for families affected by SDS; www.sickkids.ca/mediaroom/custom/SDSgeneQA.asp.

Clinical information for paediatricians in the UK

This can be obtained from the authors.

Peter Dale is a Consultant Paediatric Gastroenterologist in Newport. Georgina Hall is a Consultant Paediatric Haematologist in Oxford (both are members of the Medical Advisory Board of SDS (UK)).

John Dodge is an Honorary Professor of Child Health in Swansea and chairs the Medical Advisory Board of SDS (UK).

Authors' affiliations
G W Hall, Paediatric Haematology/Oncology Unit, John Radcliffe Hospital, Headington, Oxford, UK
P Dale, Department of Paediatrics, Royal Gwent Hospital, Newport, Gwent, UK
J A Dodge, Department of Child Health, University of Wales Swansea, Singleton Hospital, Swansea, UK

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