Rare disease

Pregnancy in Shwachman-Diamond syndrome: a novel genetic mutation with minimal consequence

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Summary

Shwachman-Diamond syndrome (SDS) is a rare inherited bone marrow failure syndrome, characterised by neutropenia, exocrine pancreatic dysfunction and often skeletal abnormalities. To date, and to our knowledge, we report a novel genetic mutation in SDS that, we believe, is associated with minimal consequence, and report the fertility and pregnancy in this individual.

BACKGROUND

Shwachman-Diamond syndrome (SDS) is an autosomal-recessive disease characterised by exocrine pancreatic insufficiency and bone marrow dysfunction.^{1 2} It is a rare disease with an estimated incidence rate of only 1 in 75 000 births, and is the third most common inherited bone marrow failure disorder after Fanconi anaemia and Diamond-Blackfan anaemia.³ About 90% of cases are associated with mutations in the SBDS gene on chromosome 7q11.^{4 5} The specific function of this gene is yet unknown, and there remains paucity in the literature as to whether certain mutations result in different disease presentations or disease severity.^{6 7}

Common symptoms at presentation include recurrent infections and symptoms of pancreatic insufficiency, such as chronic diarrhoea and failure to thrive. Less commonly, short stature associated with bony abnormality, dental abnormalities, hepatomegaly and immune defects may occur. Diagnosis is based on clinical findings, as well as haematological findings, such as neutropenia and thrombocytopenia and exocrine pancreatic insufficiency. Haematological problems can be varied and intermittent, with subsequent challenges incurred in diagnosis.⁶ Furthermore, haematological abnormalities, such as thrombocytopenia, can lead to fatal bleeding, which may lead to medical complications, especially in high-risk situations, such as surgery and pregnancy.

It is known that pregnancy in patients with bone marrow failure syndromes is uncommon, with only one case of pregnancy in SDS documented in the literature to date.⁸ Although reasons are likely multifactorial, it should be noted that fewer than 25% of reported SDS cases reached the age of 16 or more.⁸ Reports of mortality remain varied, with some reports suggesting a median survival of 35 years of age.⁹

We present a case of SDS where a likely novel genetic mutation presents with clinically milder symptoms, and report the course of fertility and pregnancy in this individual.

CASE PRESENTATION

A 31-year-old Caucasian primigravida presented at age 18 to the haematology team following a prolonged history of

pancreatic insufficiency and intermittent episodes of neutropenia and thrombocytopenia. At time of review, she was under the care of the gastroenterologists with malabsorption and pancreatic insufficiency, diagnosed by positive pancreolauryl test. This was on a background childhood history of chronic diarrhoea, steatorrhoea, malabsorption, failure-to-thrive and recurrent urinary tract infections. Sweat tests were negative in childhood, and a mild anaemia, and intermittent neutropenia and thrombocytopenia were noted. Of note, she had required Creon in her early teenage years, but this had been stopped without consequence. A clinical diagnosis of SDS was suspected.

INVESTIGATIONS

At the time of presentation, she was reasonably well in herself. Examination was unremarkable. A mild neutropenia was noted, and she was on no medication that could account for this. Skeletal survey was normal. Bone marrow aspirate and trephine showed no obvious abnormality. Although no chromosomal abnormalities were noted, she had a unique genotype with a compound heterozygote for distinct mutations of the SBDS gene: maternal c.32G>A (p.Arg11His) and c.35T>C (p.Leu12Pro) and paternal c.258+2T>C. The c.35T>C (p.Leu12Pro) sequence change in exon 1 of SBDS has not been previously described.

OUTCOME AND FOLLOW-UP

She remained under the care of the haematology team with no ongoing concern. However, despite 2 years of trying (from age 28 to 30), she was unable to fall pregnant. She was seen by our endocrinology team. Her menstrual cycle was noted to be irregular, but 21-day progesterone suggested that her cycle was ovulatory. Luteinizing hormone, follicle-stimulating hormone, prolactin, oestradiol and testosterone were all within normal range. Following this appointment, she discovered she was pregnant, with no medical intervention needed. Our obstetric team was heavily involved from the first trimester given the lack of literature evidence on pregnancy course and outcome in SDS. Moreover, genetic counselling and testing were conducted, which showed that her

Figure 1 Blood result trends during pregnancy and delivery.

partner had no mutations of the SBDS gene. A low secondary glucose (2.6) was noted on a history of pancreatic insufficiency, but this required no intervention. Bloods were closely monitored each month throughout the pregnancy without complication (figure 1).

She had no acute complications through the pregnancy. Her baby boy was born at 42/40 gestation via emergency C-section (due to failure to progress). She required 2 units of Packed Red Cells post C-section, but remained well throughout. Both mother and baby are well.

DISCUSSION

This case highlights the complexities, not only in the clinical course of SDS, but also in the genetic variation that exist in the disease. It is known that the clinical course of SDS is diverse, and the essential elements needed to consider the diagnosis are reliant on the core clinical presentations of exocrine pancreatic insufficiency and bone marrow dysfunction.^{1 2} Our patient presented with the core clinical signs, however, her pancreatic insufficiency resolved spontaneously, which has been previously shown.⁵

Genetic analysis is often used to confirm the diagnosis. SDS inherits an autosomal recessive trait. The SBDS gene is located on chromosome 7q11. Genetic analysis in Caucasian patients has previously revealed two common mutations associated with SDS; the c.258+2T>C mutation at the second exon is the most frequent mutation.^{5 6 9} In our case, genetic analysis of the patient and relative revealed she was a compound heterozygote; no clonal abnormalities were detected. Prognosis is uncertain. Some reports suggest that the projected median survival age is older than 35 years for all patients with SDS. For patients whose course is complicated by aplastic anaemia and leukaemia, the median survival is significantly reduced to age 24 and 10 years, respectively. In our case, we believe that the novel genetic mutation may be responsible for the milder clinical symptoms and minimal consequences of the disease, especially in view that her brother, too, appears to have this mutation without consequence.

Although pregnancy does not in itself necessitate reporting, our case highlights, not only a relatively normal

pregnancy in SDS, but also, to our knowledge, a novel genetic mutation, which may be contributing to this. Our literature search only highlighted one case of pregnancy in SDS.⁸ Despite the potential complications that may arise, due to bleeding diathesis, structural bony abnormality and malnutrition, both our case and the previous case documented had relatively normal deliveries. Despite this, pregnancy in SDS should be managed via a multidisciplinary team and obstetric involvement should be at the earliest opportunity. Although our case had relatively stable bloods throughout pregnancy, bloods should be taken regularly (i.e. monthly) to ensure that abnormalities are acted upon appropriately. Genetic counselling should be offered to the parents as part of fertility assessment. Our patient and the baby remain well.

Learning points

- ▶ The c.35T>C (p.Leu12Pro) sequence change in exon 1 of SBDS has not previously been described.
- ▶ It is likely that this unique genotype with a compound heterozygote for distinct mutations of the SBDS gene is associated with minimal consequence in terms of high-risk medical situations.
- ▶ A multidisciplinary team should be involved in the management of patients with Shwachman-Diamond syndrome, particularly in high-risk situations, such as surgery or pregnancy.

Competing interests None.

Patient consent Obtained.

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