Management challenges in Shwachman-Diamond syndrome

Shwachman-Diamond syndrome (SDS) is a rare disorder, characterised by bone marrow dysfunction, exocrine pancreatic insufficiency, failure to thrive and skeletal abnormalities. It is most commonly diagnosed in early childhood after the development of malabsorption and neutropenia with associated risk of infection. SDS is mainly inherited in an autosomal recessive manner, with most pathogenic variants found in the *SBDS* gene. This case report describes the challenging clinical presentation of a neonate born at 35 weeks' gestation with SDS and homozygous variants in the *EFL1* gene.

Mohamed Omer[1]
Paediatric Registrar

Muna Ewadh[2]
Obstetrics and Gynaecology Registrar

Melody Grace Redman[3]
Clinical Genetics Registrar

Uma Rajesh[2]
Obstetric Consultant

Nicola Mullins[4]
Neonatal Consultant
nicola.mullins1@nhs.net

[1]Neonatal Unit, Hull University Teaching Hospitals NHS Trust
[2]Department of Obstetrics and Gynaecology, Hull University Teaching Hospitals NHS Trust
[3]Yorkshire Clinical Genetics Service, Leeds Teaching Hospitals NHS Trust
[4]Neonatal Unit, Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust

Keywords

bone marrow failure; pancytopenia; Shwachman-Diamond syndrome; EFL1; trio exome sequencing

Key points

Omer M., Ewadh M., Redman M G., Rajesh U., Mullins N. Management challenges in Shwachman-Diamond syndrome. *Infant* 2021; 17(6): 242-44.

1. Standard antenatal genetic testing does not exclude a molecular diagnosis of SDS.
2. Consider SDS in neonates with pancytopenia and possible skeletal dysplasia.

Antenatal management

A 24-year-old woman, primigravida in a consanguineous marriage, booked at eight weeks' gestation. At booking, blood tests revealed low levels of pregnancy associated plasma protein-A (PAPP-A; 0.30MoM). A routine anatomy scan at 20 weeks identified short long bones, a small cerebellum, an echogenic bowel, an atrioventricular septal defect and severe intrauterine growth restriction (IUGR; <3rd centile). The kidneys, ureters and bladder appeared normal. Invasive testing was initially declined by the parents.

A further growth scan confirmed IUGR (femur length <3rd centile) and severe oligohydramnios. Doppler assessment of the umbilical artery, ductus venosus and middle cerebral artery (MCA) were normal. There were no concerns regarding anaemia in the antenatal period at any stage with normal MCA peak systolic velocity throughout (which correlates excellently with fetal anaemia).[1]

Amniocentesis was undertaken at the couple's request at 25 weeks' gestation, which highlighted a normal quantitative fluorescent polymerase chain reaction (QF-PCR) and array comparative genomic hybridisation (CGH). The risks of a rare genetic syndrome underlying the antenatal findings were explained to the parents. The genetics and fetal cardiology team were involved. The couple were committed to the pregnancy and were supported extensively via the fetal medicine team.

Birth

At 35^{+5} weeks' gestation an emergency lower segment caesarian section was performed following pathological cardiotocography with antepartum haemorrhage. At birth the male baby weighed 1,310g (<0.4th centile; -3 standard deviations), and occipitofrontal circumference measured 31cm (50th centile). He was noted to have joint contractures, bilateral talipes, micropenis and cryptorchidism. The placental weight was 231g (<3rd centile) with hyper-coiling of vessels.

Neonatal management

Following intubation and surfactant administration at birth, this baby remained ventilator-dependent (conventional and high frequency with inhaled nitric oxide) due to a combination of lung hypoplasia and persistent pulmonary hypertension. He also required full inotropic support. He developed progressive bone marrow failure,[2] requiring multiple blood product transfusions, neutropenia and subsequently leukopenia. He was managed for febrile neutropenic sepsis. *Enterobacter cloacae* was identified in the blood. Methicillin-resistant *Staphylococcus aureus* (MRSA) and Stenotrophomonas were identified in the sputum. TORCH screening, B12/folate levels and parvovirus PCR were unremarkable.

Postnatal echocardiography showed multiple small ventricular septal defects, severe tricuspid regurgitation, mild

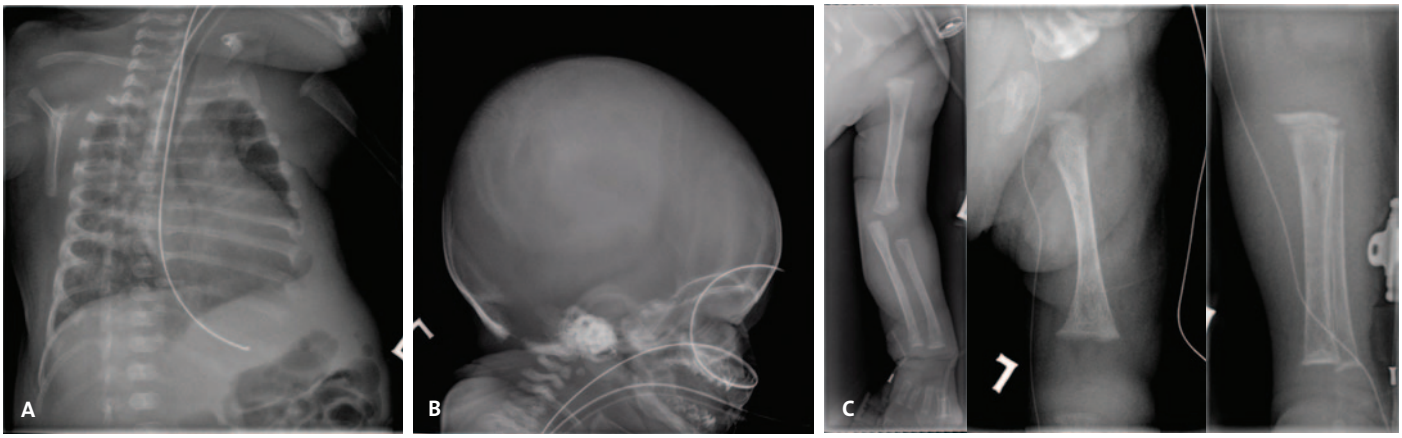

FIGURE 1 Skeletal survey findings. (A) Chest X-ray: showing abnormal ribs broadened anteriorly with cupping. (B) Skull X-ray: the skull vault is poorly ossified. (C) Limb X-rays showing shortened long bones, which are osteopenic and have irregular metaphyses.

mitral regurgitation and pulmonary hypertension. The baby was commenced on sildenafil.

He developed abdominal distension and feeding intolerance, with no surgical cause found. He remained dependent on total parenteral nutrition. His 17-hydroxyl progesterone level was normal. He had a cranial ultrasound and ophthalmological evaluation, which were normal. A skeletal survey demonstrated significant osteopenia, short long bones, a bell-shaped thorax, a poorly ossified large skull vault and abnormal broadening ribs with cupping (**FIGURE 1**). The respiratory, haematology, genetics and renal teams were involved in joint management.

His bone marrow suppression was initially considered related to the severe IUGR, placental insufficiency and bone marrow failure. A bone marrow aspirate showed aplastic marrow with low level haemophagocytosis, reduced cellularity, and undetermined bone marrow aplasia with no blast cells.

Diagnosis

Obtaining a sample for genetic testing[3] proved complex as the baby received multiple blood product transfusions. Ultimately, a skin biopsy was required. Rapid trio exome sequencing, using DNA samples from the baby and both parents, revealed a molecular diagnosis. The baby was homozygous for a likely pathogenic *EFL1* missense variant (NM_024580.5[EFL1]:c.2909G>A [p.Arg970His]), consistent with a diagnosis of SDS type 2.[4,5] Both parents carried one copy of the same variant; the baby inherited one variant from each parent.

The baby's condition acutely deteriorated on day 48 of life with severe sepsis (*Stenotrophomonas maltophilia* gram negative sepsis). He was commenced on granulocyte-colony stimulating factor (G-CSF) but sadly passed away soon after the diagnosis of SDS had been made.

Discussion

SDS is usually inherited in an autosomal recessive manner, with pathogenic variants most commonly in the *SBDS* gene.[6,7] Pathogenic variants in *EFL1* are rarely the cause, and account for <1% of SDS cases.[7] Very rarely, SDS can be autosomal dominant, for example with a *de novo* pathogenic variant in *SRP54*.[8] In this case, the *EFL1* variant inherited from each parent was identical, due to the history of consanguinity.

The parents were counselled about a 25% recurrence risk for each future child to be affected with SDS. Options such as pre-implantation genetic diagnosis or antenatal testing through chorionic villus sampling were offered. Close surveillance of future pregnancies via fetal medicine was also offered.

At the time of writing, there are at least 461 different genetic skeletal disorders, with 437 disease-causing genes identified.[9] These disorders are classified into 42 different groups; SDS falls within the 'metaphyseal dysplasia' group.[9] A proportion of these conditions may present with signs during the antenatal period. This presentation further emphasises the importance of collaboration between the fetal medicine and clinical genetics departments during the antenatal period when skeletal abnormalities are identified during antenatal scans. Couples may not wish to undergo genetic testing during pregnancy for many reasons, but the clinical genetics team can still be involved. In some cases, it may be appropriate to seek advanced parental consent for storage of DNA from a cord sample. Postnatally, collaboration between neonatology, clinical genetics, and other relevant teams is key. This approach allows phenotyping of the baby, counselling of the parents, consideration of differential diagnoses, and appropriate testing to be offered.

Lessons learnt

The lessons learnt from this care are:

1. Always store DNA prior to blood transfusions in complex settings.
2. Normal antenatal genetic testing does not exclude a molecular diagnosis.
3. Early multidisciplinary involvement from fetal medicine, obstetrics, genetics, radiology, haematology and neonatology are essential to obtaining a diagnosis enabling, for example, pre-implantation genetic diagnosis.
4. Improved communication between genetics, fetal medicine and neonatology is required.
5. Low platelets are not always directly related to IUGR.
6. Consider SDS in neonates with pancytopenia and possible skeletal dysplasia.

Parental consent

Written consent for publication was provided by the patient's parent.

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NEWS

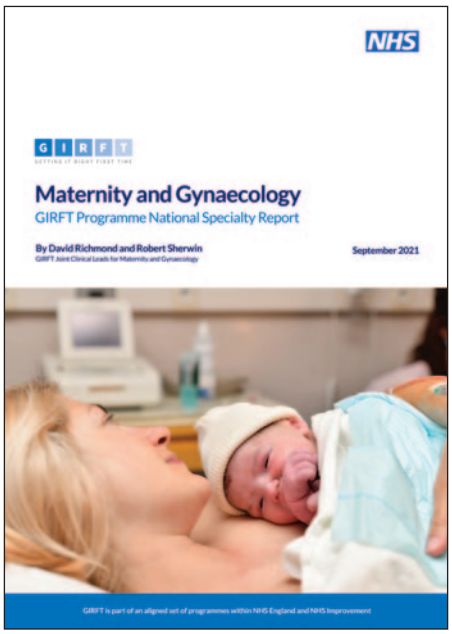
GIRFT national report for maternity and gynaecology has been published

Protecting the safety of mothers and their newborn babies, while improving women's choice and their experience of the NHS, is at the heart of the national report for maternity and gynaecology services from the Getting It Right First Time (GIRFT) programme.

The report's key recommendations for maternity care aim to reinforce the body of NHS and professional guidance that already exists to improve services for the 610,000 women who give birth in England every year and their babies. Further recommendations look at shaping a better service for women attending or admitted to hospital for a gynaecology procedure for conditions such as endometriosis, incontinence and infertility.

The report, written by GIRFT clinical leads David Richmond (former president of the Royal College of Obstetricians and Gynaecologists and a non-executive director at Birmingham Women and Children's NHS Foundation Trust, and GIRFT ambassador for south west England) and Robert Sherwin (former consultant and associate medical director at the Whittington Hospital, now a director of Women's Health Service at Auckland District Health Board), follows a review of services conducted over several years. This involved the authors visiting trust teams and analysing trust, system and national-level data to identify good practice and highlight unwarranted variations.

The GIRFT national report is aligned with and builds on existing initiatives and guidance (for example Better Births, the Saving Babies' Lives Care Bundle, the Maternity and Neonatal Safety Improvement Programme, and Each Baby Counts), highlighting the progress made to date and strengthening the delivery of



recommendations. GIRFT recommendations for maternity services include:

1. Review antenatal care ensuring schedules as outlined in NICE (National Institute for Health and Care Excellence) guidance are followed. Follow the Saving Babies' Lives Care Bundle 2 as outlined in the NHS Long Term Plan.
2. Review and act upon comprehensive maternity patient experience data.
3. Strive towards healthy BMI rates and smoking rates in line with top decile of performance.
4. Improve recording of data about key aspects of maternity care, including outcome data for mothers and babies, for example spontaneous birth, caesarean section, assisted birth.

Striving towards healthy BMI rates and smoking cessation

More than half of women whose BMI is recorded when booking in for maternity services are overweight, increasing their risk of miscarriage and stillbirth. Research also shows that around 10% of women are smokers at the time they give birth, increasing the risk of poor fetal growth, preterm birth, and respiratory problems for the baby. GIRFT is calling for integrated care systems and other partners to review the uptake of smoking cessation programmes and identify barriers to participation, and to encourage use of obesity services for women of childbearing age, to improve the health of mothers-to-be and their babies.

Improving data to inform future practice

The GIRFT review found greater variation than expected in rates of emergency and elective caesarean section, and variation in the use of induction and instrumental delivery, but there is insufficient data to inform detailed recommendations. GIRFT recommends improving the recording of data about key aspects of maternity care, including outcome data around spontaneous birth, caesarean section and assisted birth.

Litigation: brain injury at birth

The report also looks at how litigation around maternity services can be reduced. Legal claims against maternity services represent 9% of the number of claims received by NHS Resolution annually but 50% of the total value (the highest cost specialty). This is because many claims arise from brain injury at birth, resulting in the injured child requiring significant care needs for life. The report reinforces the NHS Resolution's Maternity Incentive Scheme (MIS), which incentivises the delivery of safer maternity care through the achievement of ten safety actions.