CASE REPORT

Mitral valve replacement in neonatal endocarditis: time to discuss prevention strategies for Group B streptococcus disease

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SUMMARY

Group B streptococcus (GBS) is recognised as one of the leading organisms in early-onset neonatal sepsis but is also a cause of late-onset GBS septicaemia, meningitis and rarely, infective endocarditis (IE). We report a case of a healthy term neonate who developed GBS septicaemia and meningitis having presented with parental concern and poor feeding. Subsequent identification and treatment of GBS resulted in the requirement for long-line intravascular access in order to administer antibiotic therapy. One week later, after repeated parental concern and symptoms of shortness of breath, the neonate presented to Accident and Emergency and subsequently a Paediatric Cardiorespiratory Intensive Care Unit where emergency resuscitation procedures were required and diagnosis of severe IE affecting the mitral valve was made. Mitral valve replacement was complicated with significant morbidity and prolonged hospitalisation. An innovative procedure to insert a Melody valve was successful.

BACKGROUND

Group B streptococcus (GBS) is a leading cause of sepsis in neonates; however, neonatal infective endocarditis (IE) is rare, its surgical management is challenging requiring intensive therapy and intervention, and it is associated with a high morbidity and mortality rate; the diagnosis is often made at post-mortem examination.^{1 2}

We aim to

- Raise awareness of IE in patients being treated for sepsis and the importance of early detection.
- Educate about the devastating sequelae of GBS disease and the significant surgical challenges of mitral valve replacement in infancy.
- Inform readers of a new innovative Melody Valve replacement for mitral valve disease.
- Highlight the need for a national maternal screening programme for GBS as part of preventative strategy for neonatal GBS.

CASE PRESENTATION

A term male infant was born in good condition by spontaneous vaginal delivery following an uneventful pregnancy with normal antenatal scans and protective maternal serology as tested in keeping with UK screening in pregnancy, negative for HIV, hepatitis B and syphilis. Mother and baby were discharged home the following day after a normal newborn examination. Mother does not recall having been unwell but had an intrapartum swab

taken, that would later confirm GBS, but she was not told of the positive result, and it was not in her discharge papers for the community midwives to follow up.

The infant presented to Accident and Emergency (A&E) on day 6 of age with a few days history of poor feeding, jaundice and lethargy. He was discharged and again presented 24 hours later with the same history. He was reviewed and discharged to community midwifery care with a feeding plan and weight monitoring as part of management for suspected physiological jaundice and feeding difficulties.

On day 16 of age, he again presented to A&E with a 2-day history of fever and irritability and was treated for suspected septicaemia with ceftriaxone on admission. Initial C reactive protein was <1 mg/L, but in the following day, it rose to 111 mg/L. A venous blood culture grew Group B streptococci sensitive to penicillin and ceftriaxone (MIC 0.064 and 0.125, respectively). A lumbar puncture was performed after the start of antibiotic therapy, and cerebrospinal fluid showed 300 white cells, of which 80% were polymorphs, with no bacterial organisms on microscopy, negative 16S and viral PCR. He was diagnosed with invasive GBS septicaemia with meningitis, and antibiotics were changed to intravenous benzylpenicillin and gentamicin. He was discharged home after 5 days, with a peripheral intravenous long-line in situ for ambulatory antibiotics, given at home during the day and the evening dose in hospital, with the plan to complete a total of 3 weeks treatment. While ambulating, he was reviewed by nursing staff who checked his observations prior to giving antibiotics each evening and by community nurses at home for the morning dose.

On day 26 of age, 10 days into his treatment for meningitis, he re-presented to A&E with respiratory distress, lethargy and poor feeding. On clinical assessment, he was found to be tachypnoeic, with a new cardiac murmur, an enlarged liver, peripheral and central mottling and a rising lactate. He was transferred to the Paediatric Cardiorespiratory Intensive Care Unit (PICU) at Royal Brompton Hospital by the Children's Acute Transport team for management of heart failure.

On admission to PICU, he was confirmed to have signs of severe cardiac failure with a 3/6 systolic murmur at the left lower sternal edge with normal first and second heart sounds, cool peripheries, an enlarged liver of 3 cm and moderate

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subcostal recessions. Despite inotrope treatment with milrinone, his cardiac function continued to deteriorate with a lactate peaking at 11 mmol/L, increased work of breathing and tachypnoea, and he required emergency intubation and ventilation.

INVESTIGATIONS

A transthoracic echocardiogram was performed on admission and showed two mobile echogenic masses attached to each of the mitral valve leaflets with severe mitral regurgitation and right ventricular dysfunction (figures 1 and 2). The appearance was consistent with IE with vegetations measuring 9.2×3.6 and 3.8×3.2 mm. The heart appeared otherwise structurally normal with a small atrial septal defect.

Following diagnosis of IE, further investigation included ophthalmology review, renal ultrasound scan and CT scan head, each confirming no evidence of septic emboli.

Following surgical mitral valve replacement, a tissue sample sent for histology of the mitral valve subsequently revealed fibrosing granulation tissue with patchy haemorrhage, focal myocyte necrosis and few Gram-positive cocci, findings consistent with bacterial endocarditis. PCR later confirmed GBS on 16sr DNA sequence *Streptococcus agalactiae*.

TREATMENT

In the first 12 hours of his PICU admission, he developed abdominal distension with features of necrotising enterocolitis (NEC) suspected to be mesenteric artery septic embolisation. He was kept nil by mouth, and metronidazole was added to his antibiotic regimen (gentamicin and cefotaxime) for gut microbial cover.

Surgical repair of his mitral valve was delayed until his abdomen was clinically stable. During that time, he remained sedated, paralysed and ventilated, receiving total parental nutrition, fluids, albumin replacement for losses and antibiotics. In discussion with microbiology colleagues, his antibiotic regime was rationalised to cefotaxime (50 mg/kg four times a day), gentamicin and vancomycin for a planned 6-week course in view of invasive disease and with higher trough levels of vancomycin as per local antimicrobial policy for endocarditis. Metronidazole, which had been started in view of features of NEC, was discontinued following a 10-day course and once his abdomen had clinically stabilised.

Despite optimised antimicrobial therapy and now negative blood cultures, the vegetations did not show significant change, and his cardiac function continued to be severely compromised by the mitral valve disease. Following careful consideration

Figure 2 Four-chamber 2D echocardiogram with Doppler demonstrating regurgitation across mitral valve.

between paediatric intensivists, cardiologist and cardiothoracic surgeons, it was concluded that surgery with intention to repair or replace the valve was the best option. He went to theatre on day 34 of life, 8 days after admission to PICU, and was found to have large flailing segments of mitral valve with ruptured chordae. Two attempts at repair of his valve were made but were not successful. A mechanical prosthesis—a 17 mm St Jude's Valve—was therefore placed during the same operation, and his sternum was left open postoperatively. He was on an anticoagulation protocol postoperatively in view of the mechanical valve with regular monitoring of antiXa level and APTT until coagulation was stable and within therapeutic range.

Twelve days after chest closure, at 53 days of age, he was successfully extubated and on full feeds. Cardiac echo at this time demonstrated good movement of prosthetic valve discs and improving biventricular function.

Eight weeks after prosthetic valve placement, he developed increased left atrial pressures with significant pulmonary oedema, requiring emergency intubation and ventilation and inhaled nitric oxide. On echo, there was evidence of thrombus formation on his prosthetic mitral valve (figure 3). He received thrombolysis therapy overnight and went to theatre for emergency exploration the following day. In theatre, his mitral valve was found to be working well and no clots were seen. Clinical deterioration recurred 48 hours later, and echocardiography showed evidence of clot on the prosthetic valve once again, and

Figure 1 Four-chamber view on 2D echocardiogram showing mobile, echogenic vegetations on leaflets of the mitral valve, bulging into left atrium and left ventricle.

Figure 3 Echocardiogram with Doppler demonstrating regurgitant flow across the thrombosed mechanical St Jude's valve.

he required emergency surgery. On each occasion, blood cultures were taken and no positive bacterial growth found. Intraoperatively, clots were this time seen to be impeding the opening of the mural leaflet of his valve, and so it was replaced with a same-sized St Jude prosthetic valve, with good movement of the new valve leaflets confirmed on transoesophageal echo. Postoperatively, he developed rhythm disturbance with supra-ventricular tachycardia and ectopics, requiring amiodarone therapy.

Despite appropriate anticoagulation as per our local policy and monitoring, our infant continued to have episodes of valve obstruction of this second prosthetic valve secondary to thrombi. After extensive discussion of the multidisciplinary team, it was decided to replace his valve with a Melody Valve. The Melody Valve is a bovine jugular vein valve mounted on a stent. It was primarily designed to be implanted percutaneously in the pulmonary position but has recently been used surgically as a replacement of the mitral valve in infants as a last resort rescue procedure. This was planned in conjunction with Dr Emani from Boston Children's hospital who had experience with this innovative procedure.³ He underwent a fourth surgery at 8 months of age and had successful replacement of the St Jude's for a Melody Valve in the mitral position, inserted by open cardiac surgery (figure 4).

Significant postoperative complications included bleeding that required chest exploration and delayed chest closure, low cardiac output necessitating high inotrope support and chylothorax that was managed with chest drain and total parental nutrition, later changed to modular feeds. He also had marked deterioration in his renal function, resulting in significant third-space fluid losses and required peritoneal dialysis. Further complications arose from rhythm disturbance with atrioventricular dissociation needing dual-chamber pacing mode in the immediate postoperative period and started on amiodarone. He continued to be in atrial rhythm with no haemodynamic compromise, and cardioversion was carried out, which cardioverted to sinus rhythm for few days but again reverted back to atrial rhythm. Propranolol was added, but he stayed in haemodynamically stable atrial rhythm. The new Melody Valve did not require an anticoagulation regimen, and there were no thrombotic complications encountered.

Figure 4 Chest X-ray with Melody Valve in the mitral position.

Extubation was possible 4 weeks after Melody Valve placement at 9 months of age, although he still required non-invasive ventilator support. An abnormal breathing pattern was noted, confirmed to be paradoxical diaphragmatic movement of the right side on ultrasound scan, and he required diaphragm plication, following which, he was extubated onto non-invasive ventilation. Despite the significant complications associated with multiple cardiac surgery for valve replacement and severe morbidity that he has endured as a result of valve destruction from endocarditis, with the Melody Valve he was finally able to make a recovery without recurrent valve obstruction or complications of anticoagulation and maintains good cardiac output. We are pleased to report that our patient has now been successfully discharged, and he is under regular review and followed up with the cardiology team.

OUTCOME AND FOLLOW-UP

This previously healthy term neonate with no evidence of underlying cardiac disease has endured bacterial valve destruction and subsequent significant morbidity as a result of postoperative complications associated with mitral valve replacement:

1. There is evidence of intracranial pathology, the long-term implications of which are currently unknown. Postoperative cranial ultrasound 2 weeks after his Melody Valve replacement indicated the presence of a small extra-axial collection. CT brain showed that the fluid is of an intermediate density consistent with a chronic subdural haematoma (figure 5). He shall require future community-based follow-up in order to assess the consequences of these findings on his neurodevelopment.
2. Significant feeding and swallowing dysfunction is noted, attributed to bulbar palsy identified on neurophysiology testing, and as such he has required percutaneous endoscopic gastrostomy tube insertion.
3. Right-sided hemidiaphragm denervation has been demonstrated, and together with a persistent requirement for non-invasive ventilation, he has subsequently required tracheostomy.

Figure 5 CT head demonstrates bilateral subdural haemorrhages.

- There is likely to be a need for further mitral valve intervention or surgery such as re-dilation in the future.

This case has also led to an internal review of practice at the infant's local hospital.

DISCUSSION

Our case highlights the aggressive nature of GBS sepsis, its potentially fatal complications and the need for clinicians to remain vigilant for these complications even when treatment has been started.

On review of the literature, although there are published cases of neonatal IE, reports of GBS endocarditis are rare, and in particular with such a complex surgical course.⁴ Current literature suggests a change in the epidemiology of IE in children with increasing cases occurring in those without pre-existing heart conditions and *Staphylococcus aureus* being the more common infective organism.⁵⁻⁷

Most organisms that cause paediatric IE are Gram-positive cocci, streptococci, staphylococci and enterococci. The marked predominance of mitral valve lesions⁸ may be due to the greater stress forces on the mitral valve than on the other cardiac valves, as reflected by the resting pressure at the time of valve closure. Alternatively, a patent foramen ovale or an atrial septal defect could have been responsible for the shunting of septic thrombi from the right to left side, which our patient was seen to have at surgery.

Some of the early clinical features of IE in a neonate are variable, non-specific and indistinguishable from septicaemia.^{1 2} Septic embolic phenomena are common, resulting in osteomyelitis, meningitis or pneumonia. Neonates with IE often have feeding difficulties, respiratory distress, tachycardia, a new or changing heart murmur and hypotension. Many neonates with IE may develop neurological signs (seizures, hemiparesis or apnoea).

Once treatment is started with high-dose antibiotics, mortality remains high, reported at 25–60%, but could possibly be decreased further if early diagnosis is made.⁷ Common indications for surgery include progressive cardiac failure, valvular obstruction, perivalvular extension of infection, fungal endocarditis, persistent bacteraemia despite appropriate antibiotic therapy and significant embolic events, especially when the aortic or mitral valve is involved.⁴

It is estimated that about 1 in 2000 babies born in the UK and Ireland develops early-onset GBS infection. This means that every year in the UK (with 680 000 births a year), around 340 babies will develop early-onset GBS infection. The Royal College of Obstetrics & Gynaecology guidance does not currently recommend a screening programme of tests to pregnant women specifically to check for Group B strep carriage during late pregnancy, unlike in the USA.^{9 10} The agreed practice in UK hospitals and supported by National Institute of Clinical Excellence guidance is to offer intrapartum antibiotics to women who have identified GBS colonisation in order to protect the baby from invasive GBS disease.¹¹ The latest Cochrane review identified a lack of sufficient trials for screening and prophylaxis.¹²

In light of the significant morbidity and complications that arise from GBS disease, we believe preventative measures are needed. Screening that identifies women who require prophylactic antibiotics for prevention of newborn sepsis also encourages increased awareness of GBS and the potential of late-onset disease, information that is important for parents and carer to help them identify early signs of illness. In this case, we reflected on the great value of parental concern that brought the infant's illness to the attention of health professionals on day 16 of

life where his symptoms were not just related to feeding difficulty, but also a sign of sepsis. As health professionals, the importance of listening to parental concern as part of clinical decision-making and to improve patient safety is widely acknowledged,^{13 14} and we believe that further empowering parents with clear advice about GBS detected through screening is important.

We also recognise the pressure to manage many children on antibiotics through ambulatory care in the community.

Patient's perspective

The parent's perspective, a recollection of events from treatment of meningitis to re-presentation to A&E, was described by his mother and transcribed.

- ▶ My son and I had been in hospital for 5 days as he was being treated with antibiotics for meningitis, and this was the first time I'd heard about GBS. We were then discharged to continue antibiotics at home with his long line in his arm and to come in for evening doses to the ward. I felt cautious, but everyone reassured me that he was ok. Looking back I didn't think he was quite right, but we went home. Every night we came back to the ward to have drug levels taken and for his evening dose, and on one occasion, his long line needed re-dressing and we were seen by a doctor, but otherwise it was only a nursing check. Each night the nurses did his observations and told me everything was fine. Then one morning, after we'd been to hospital the night before and he's had his antibiotics, we thought he looked unwell and was breathing fast. The community nurse who came to give his morning antibiotics said we should go to A&E and it might be dehydration, so we called a taxi. I felt his hands and it was a hot Summer's day, but his hands and feet were freezing and I could see he was breathing so fast.
- ▶ Once we got to A&E, the nurses were trying to do his observations and had to keep repeating them. I was worried, he looked so unwell and I asked to see a doctor, but they said he's fine and would be seen soon. I got more and more anxious and got angry as he was turning blue and they were still trying to do a blood pressure. A doctor passing by heard me and saw my son; then, he scooped him up and said that they were going to Resusc. I'm still traumatised that my son was crashing in my arms, and I was completely helpless and felt that no one was listening to me, just talking among themselves. I saw him put on the trolley in the Resusc room, and no one told me what was happening, and I thought I'd lose him.

Following the interview, the patient's mother has raised the following points she'd like the professionals to learn from:

- ▶ Transparency about doing investigations, she wishes she'd known about the swab, why it was performed, the result, known about GBS, and known what to look for.
- ▶ She felt that she was complacent about how ill her son was because no one really seemed to take her concerns too seriously, and she was continuously reassured.
- ▶ She wanted the team to be honest about what had been missed and to help her understand what was wrong with her son.
- ▶ She felt that his deterioration with endocarditis had not been foreseen and that she had not been prepared for the possibility of complications.

However, in view of the complications such as IE, we recommend that regular clinical assessment is essential as only by maintaining a high index of suspicion with early recognition and aggressive management of endocarditis, there may be improved mortality and morbidity. We suggest that clinicians should always be mindful of the possibility of endocarditis when treating sepsis and for echocardiography be considered in those infants particularly with central lines or clinical findings of new or changing murmurs. In the case discussed, we considered that earlier detection of IE may have been possible through regular and thorough medical assessment that was less accessible once the patient was discharged for ambulatory treatment.

Learning points

- ▶ Neonatal Group B streptococcus (GBS) disease can lead to potentially fatal complications including endocarditis.
- ▶ Clinicians should have a high index of suspicion for infective endocarditis (IE) when treating sepsis particularly for those infants with central lines, and consider echocardiogram as only with early recognition and management of IE can morbidity and mortality be improved.
- ▶ Screening for GBS is not recommended by the UK National Screening Committee nor the Royal College of Obstetricians & Gynaecologists, whereas it has a high profile in the USA where the Centres for Disease Control and Prevention recommends routine screening and treatment for all pregnant women, and we suggest this should be so in the UK.
- ▶ Treatment of endocarditis in infants is complex and multifaceted with complications arising from septic emboli and technical challenges of mechanical valve replacement.
- ▶ Management of infants ambulating on antibiotics for treatment of known sepsis should include regular medical assessment of the patient for complications.

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