Multidisciplinary Team Approach Is Key for Managing Pregnancy and Delivery in Patient with Rare, Complex MPS I

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Received: 30 June 2015 / Revised: 30 November 2015 / Accepted: 04 December 2015 / Published online: 27 February 2016
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Abstract A 23-year-old primiparous lady (Ms S) was referred to preconception clinic with known Hurler–Scheie syndrome (mucopolysaccharidosis 1). Ms S had been under the care of the adult inherited metabolic disorder physicians prior to becoming pregnant. She and her partner received prenatal counselling and following spontaneous conception was closely managed by a multidisciplinary team involving foetomaternal obstetricians, anaesthetists, cardiologists, geneticists and endocrinologists in two tertiary referral hospitals throughout her pregnancy. She went on to deliver a live male child at 37/40 by elective caesarean section. As far as we are aware, this is the first case report of a term pregnancy in a woman with moderate to severe mucopolysaccharidosis 1 (MPS 1).

Introduction

A literature search was performed to identify any publications on pregnancy management in patients with MPS 1. The databases MEDLINE, CINAHL, Cochrane

Library, DUETs, NHS Evidence and DynaMed were reviewed with the MeSH terms ‘treatment AND/OR management’, ‘pregnant females’ and ‘mucopolysaccharidosis’. One case report described a 32-year-old lady with attenuated MPS 1 who had been on laronidase replacement therapy for 3 years prior to conception of her second child. She went on to have a live male child who was breastfed for 3 months. No laronidase was detected in her breast milk, and the infant did not develop any adverse drug-related events by 2.5 years of age (Castorina et al. 2015). There were no further papers documenting management of pregnant patients with moderate to severe MPS 1. Eleven patients with MPS 1 on the specialist registry are also known to have become pregnant to date, but their outcomes and management have not been disclosed.

Hurler–Scheie syndrome (MPS 1) is a rare autosomal recessive condition affecting 1.07/100,000 births in the UK (Moore et al. 2008). It occurs in individuals with a lysosomal enzyme alpha-L-iduronidase deficiency secondary to a defective iduronidase alpha (IDUA) gene (4p16.3) on chromosome 4. Alpha-L-iduronidase catalyses the metabolism of glycosaminoglycans (GAGs), and its deficiency leads to GAG accumulation in the cells and connective tissues of sufferers. With time it causes irreversible damage to tissues throughout the body and, depending upon the degree of severity, impedes on the functioning of the bones, corneas, skin, cartilage, tendons and vital organs. MPS 1 clinically manifests as a continuous spectrum of symptoms but can be divided into three broad types with overlapping features as follows:

Communicated by: John H Walter, MD FRCPCH

Competing interests: None declared

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Type	Severity	Age of onset	Presentation
Scheie syndrome	Mild	5 years	Normal intelligence/mild learning disability, corneal opacification, glaucoma, retinal degeneration, carpal tunnel syndrome, deformed hands/feet, short neck, valvular heart disease and obstructive and restrictive airway disease. Patients usually survive to adulthood (Campos and Monaga 2012; Saudubray et al. 2012)
Hurler–Scheie syndrome	Moderate	3 years	Moderate learning disability, hearing loss, corneal opacification, coarse facial features, short stature, small jaw, progressive joint stiffness, compressed spinal cord, valvular heart disease, umbilical hernia, recurrent respiratory tract infections, obstructive and restrictive airway disease and sleep apnoea. Patients may survive to adulthood (Campos and Monaga 2012; Saudubray et al. 2012)
Hurler syndrome	Severe	1 year	Progressive mental decline, loss of physical skills, speech impairment, hearing loss, enlarged tongue, corneal opacification and retinopathy, carpal tunnel syndrome, restricted joint movement, inguinal or umbilical hernia, short stature, distinct facies (flat face, low nasal bridge, prominent forehead), hepato-/spleno-/cardiomegaly, recurrent ear and respiratory tract infections and obstructive airway disease. Mean survival time 9 years (Moore et al. 2008)

Enzyme replacement therapy slows the progression of MPS 1, but there is currently no cure. Those with milder forms such as Scheie syndrome may consider starting families should they reach adulthood. Yet the physiological changes associated with pregnancy render the patients high risk obstetrically. The collaborative input of multiple medical specialties is important therefore to counsel and monitor progression of these patients throughout pregnancy.

Background

Ms S was diagnosed in childhood with moderate to severe Hurler–Scheie syndrome. She had a short stature with a BMI of 27, coarse facial features, a restricted airway and contracted pelvis. She had asthma, mild to moderate mitral and aortic regurgitation and stenosis and occasionally suffered from migraines. As a child Ms S required the insertion of a right grommet and left ventilation tube to manage recurrent episodes of non-suppurative otitis media and sensorineural hearing loss. She also had surgery for decompression of her wrist for carpal tunnel syndrome, an umbilical hernia repair, tonsillectomy and adenoidectomy and a cervical spine fusion using a morphogenic bone graft. She had received a weekly enzyme infusion of Aldurazyme 5,500 international units through a portacath to slow the progression of her condition for over 10 years. Ms S was blood group A positive and had no known drug allergies.

Prior to becoming pregnant, Ms S had been under the care of the adult inherited metabolic disorder physicians. Together with her husband (who was diagnosed with retinoblastoma as a child), she received robust prenatal counselling following multidisciplinary team input from foetomaternal obstetricians, anaesthetists, cardiologists, geneticists and endocrinologists regarding the following:

1. *Grown-up congenital heart disease in pregnancy*

Cardiac output increases 30–50% (increase in blood volume and heart rate principally peaking in the second trimester) in pregnancy, and patients with congenital heart disease (CHD) are at 5% risk of mortality, 3–5% risk of CHD (albeit in Ms S's case, her cardiac disease was part of the constellation of symptoms associated with her autosomal recessive condition) and growth restriction in the offspring. Ms S had a satisfactory echocardiogram preconceptually therefore upon review with the cardiologist and obstetrician; plans were made for a repeat echocardiogram and foetal echocardiogram at 24/40, serial foetal growth scans from 28/40 and regular reviews to check for signs of cardiac decompensation (Steer et al. 2006; Guyton and Hall 2005).

2. *Uncertainty of teratogenicity of enzyme replacement therapy*

Ms S was counselled regarding the unknown effects of laronidase on the foetus, although there are amassing reports of no overt harm to foetuses (Castorina et al. 2015; Wendt et al. 2005; Giannubilo et al. 2015). What's more, given the risk of her condition worsening without treatment, the decision was made to continue on medication and have regular foetal surveillance.

3. *Contracted pelvis and hip joints*

The rise of oestrogen and relaxin cause remodelling of connective tissues resulting in increased laxity of joints (particularly sacroiliac and pubic symphysis) (Ostgaard et al. 1991). However, as Ms S had a contracted pelvis, she was at high risk of an obstructed labour. Consequently following discussion with the multidisciplinary team, it was agreed Ms S should have an elective caesarean section (CS) at 37/40 after receiving steroids.

4. *Anaesthetic difficulties due to her previous cervical vertebra fusion and difficult airway*

Ms S previously had a grade 4 laryngoscopy when requiring general anaesthesia. Her risk of a difficult intubation would be further compounded by pregnancy-induced weight gain, breast enlargement, progesterone-associated respiratory tract mucosal oedema and capillary engorgement (Jouppila et al. 1980). Hence, a decision was made for a combined spinal and epidural (CSE) anaesthetic for rapid onset and sustained pain relief if surgery was prolonged. In the event of failure or complications of regional anaesthesia, an awake fiberoptic intubation (AFOI) was planned to secure her airway for general anaesthesia for the CS.

5. *Increased risk of respiratory impairment*

Forced vital capacity (FVC) and peak expiratory flow rate (PEFR) normally increase by the second trimester (Grindheim et al. 2012). However, as in a study majority of gravid patients with restrictive lung disease had a stable FVC (and Ms S did not require NIV preconceptually) (Lapinsky et al. 2014); Ms S was managed expectantly for her respiratory symptoms.

6. *Her husband had retinoblastoma*

Upon advice from the paediatricians and geneticists, a plan for cord blood samples at delivery and having an early eye examination by an ophthalmologist was decided to check for the autosomal dominant condition

retinoblastoma in the neonate (Ms S's condition is a rare autosomal recessive condition therefore highly unlikely to be passed on).

Case Presentation

At 7 + 5/40, Ms S, a 23-year-old primiparous lady with Hurler–Scheie syndrome, presented to a tertiary women's hospital following spontaneous conception. She was subsequently seen by a foetomaternal specialist every 4 weeks from 12 + 5/40 until delivery. She had a baseline sinus tachycardia of 130 beats per minute, a mild soft pansystolic murmur, and signs of restrictive lung disease. Bedside tests of her airway revealed poor mouth opening but with a natural inter-incisor gap, large tongue and inability to protrude her lower jaw due to a receding chin. There was no neck extension as a result of previous cervical spine fusion. She complained of worsening snoring as the pregnancy progressed. At 26 + 5/40 she had symptoms suggestive of symphysis pubic dysfunction for which she took simple analgesia but declined physiotherapy. In the last week of her pregnancy, she developed a lower respiratory tract infection which was treated with oral amoxicillin.

Investigations

Ms S had normal routine booking bloods. Her cardiac output and size remained stable upon repeat echocardiogram at 24/40, so no further specialist cardiologist input was required antenatally.

Nasoendoscopy confirmed a good sized laryngeal inlet and flattened epiglottis. Spinal MRI revealed that she had effacement of the anterior and posterior CSF column in the cervical spine region but normal anatomy of the thoracolumbar spine.

The foetal Down's risk was 1:44,000 (through quadruple testing) and had a normal echocardiogram and mid-trimester anomaly scan. Its growth from 26 + 5/40 was above the 50th centile.

Treatment

At 37/40, Ms S was admitted for an elective CS. Two units of blood were crossmatched and intraoperative cell salvage

set up as a prophylactic measure given the uncertain effect of uterotonics in MPS 1 patients. An intensive care (ITU) bed at a neighbouring tertiary hospital was booked to provide post-operative ventilatory support in the event of general anaesthesia. She was initially anaesthetised via CSE using 300 micrograms of diamorphine and 2.2 ml of 0.5% hyperbaric bupivacaine. The initial spinal attempt produced a sensory block level to L1. This was inadequate for surgery so the epidural component was topped up over 10 min to try and achieve the necessary block height to T4. Thirty-five minutes after commencing the epidural top-ups, the block height remained at T10. A second spinal anaesthetic was performed using 1 ml of 0.5% hyperbaric bupivacaine and achieved a block to T4. A consultant maxillofacial surgeon was present during the surgery in case the AFOI failed, and an emergency tracheostomy was necessary. The CS proceeded, and a live male child was delivered with no intraoperative complications. Biosynthetic sutures were used to close the uterus in two layers for adequate haemostasis, and cord blood samples were taken at delivery.

Outcome

Ms S was managed on a high dependency unit for 2 days following CS and was then transferred to a postnatal ward. She had a successful trial without urinary catheter 48 h post-surgery and was discharged on prophylactic oral antibiotics for 7 days and low molecular weight heparin for 6 weeks.

Learning Points

- Multidisciplinary team management of patients with MPS 1 is crucial for successful pregnancies and is best managed by a team with expertise in their fields. The successful outcome of pregnancy in this complicated patient was facilitated by the medical, obstetric and anaesthetic teams with input from the patient.
- If patients with MPS 1 require surgery, input from the ear, nose and throat surgeons, anaesthetists and ITU physicians is advised during the planning stage as induction of anaesthesia, intubation and post-operative respiratory recovery can be problematic.
- Pre-pregnancy counselling for women with MPS 1 should include detailed discussion of the potential complications of each stage of pregnancy and delivery, taking into account the stage of disease and the availability and technical abilities of the medical teams involved.

Acknowledgements Many thanks to Tony Whitehouse and Katherine Pearce for their help with this paper.

Compliance with Ethics Guidelines

Conflict of Interest

Joy Troko, Yasmin Poonawala, and Bill Martin declare that they have no conflict of interest. Tarekegn Geberhiwot has served on the Genzyme advisory board and has received service development and travel grants. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

Informed Consent

The patient gave consent for her information to be published.

Contribution of the Authors

Mr Bill Martin was the lead obstetrician involved in the patient's antenatal care and delivery. Dr Tarekegn Geberhiwot was the primary physician for the patient prenatally and was involved in the decision making throughout the patient's pregnancy. Dr Yasmin Poonawala was the consultant anaesthetist who anaesthetised the patient for surgery and was involved in the planning of delivery for the patient. Dr Joy Troko is a trainee obstetrician who assisted in the delivery of the patient and submitted the case for publication. All authors listed were involved in writing the report.

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