Osteopetrosis in pregnancy: a rare case report

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Summary: Osteopetrosis is a genetic syndrome characterized by the failure of osteoclasts to resorb bone. This leads to skeletal fragility despite increased bone mass, with fractures, dental abscesses, osteoarthritis and scoliosis being the most common complications. There are few reports of patients with type II osteopetrosis undergoing pregnancy and delivery. This case outlines the management of pregnancy and a successful delivery in a woman with this rare condition.

Keywords: osteopetrosis, Albers-Schoenberg disease, marble bone disease, pregnancy

INTRODUCTION

Osteopetrosis was first described by the German radiologist Albers-Schoenberg, in 1904 and is a sclerosing skeletal dysplasia.¹ It is sometimes referred to as 'marble bone disease'. In this genetic syndrome osteoclasts fail to resorb bone, which leads to skeletal fragility despite the increase in bone mass. Further symptoms include haemopoietic insufficiency, disturbed tooth eruption, nerve entrapment syndromes, osteomyelitis and growth impairment. The incidence is estimated at 1:100,000–500,000.^{2,3}

In humans, three distinct forms of osteopetrosis are distinguished, based on age of onset and clinical features. These are adult-onset (autosomal-dominant inheritance, also called ADO or Albers-Schoenberg disease), intermediate (autosomal-recessive, also called IRO) and infantile osteopetrosis (autosomal recessive, also called ARO).^{4,5} ADO is the most frequent form of osteopetrosis, with an incidence estimated at 5:100,000.⁵ While adult or late onset osteopetrosis is associated with good long-term survival rates and is very rarely fatal, infantile osteopetrosis results in death within the first 10 years of life, mainly due to severe anaemia, bleeding or infection.^{2,3}

On the basis of radiographic, biochemical and clinical features, two types of adult-onset osteopetrosis are described: type I and type II. Type I has been linked to genetic mutations in *LRP5* (low-density lipoprotein receptor-related protein 5; locus 11q13.4), and type II to mutations in *CLCN7* (osteoclast-specific chloride channel pump; locus 16p13).^{4,6,7} *CLCN7* mutations have been found in 75% of type II cases of the disease.^{2,6} This gene controls the ruffled border (a complex area of folding of the osteoclast membrane) chloride conductance of osteoclasts, which is needed to ensure bone resorption. There is no gender preference and while anticipation does not occur in successive generations, penetrance can be incomplete (reported at 60–90%) and phenotypic variability is reported

within families.^{2,6,7} The proportion of cases caused by *de novo* mutations is not reported.⁶ Further, several heterogeneous molecular or genetic defects can result in impaired osteoclastic function and the exact molecular defects or sites of these mutations are largely unknown.²

In osteopetrosis, the bone cortex and cancellous bone cannot be distinguished radiologically. Osteopetrosis type I is characterized by generalized osteosclerosis most pronounced in the cranial vault. Patients are often asymptomatic, but some suffer from pain and hearing loss. It appears to be the only type of osteopetrosis not associated with an increased fracture rate and as a result some experts have suggested reclassifying this as a 'high bone mass' disease.^{2,4} In contrast, osteopetrosis type II is frequently symptomatic with 80–90% of patients experiencing clinical manifestations, usually increasing after 20 years of age.^{4,5} Radiologically, it is characterized by sclerosis, predominantly involving the spine (a typical sandwich-like appearance of the vertebrae is described), the pelvis and the skull base. Fragility of bones, leading to increased frequency of fractures, and dental abscesses are the major complications, but patients also commonly develop hip osteoarthritis and scoliosis. Osteomyelitis of the mandible is often associated with dental caries, but septic osteitis or osteoarthritis at other locations can also occur.⁶ Increased rates of postsurgical complications are also reported, with delayed union or non-healing of fractures and infection. Gene carriers are not known to have an increased risk of disease manifestations, but have been shown to have significant increases in bone mineral density.⁴ Haematopoietic stem cell transplantation is performed only for the most severe forms of osteopetrosis (ARO). There is no specific treatment for osteopetrosis.

CASE REPORT

A 27-year-old woman booked at 11⁺⁵ weeks gestation in her first pregnancy which was unplanned. She was diagnosed with osteopetrosis at the age of six, following multiple fractures affecting her lumbar spine and long bones, and went on to

experience multiple pelvic, vertebral and long bone fractures throughout childhood. Unusually, she had no fractures since the age of 21, and prior to pregnancy worked full-time and was physically active. While well-educated about her disease, she had never pursued genetic counselling. There was a relevant three-generation family history, and so the autosomal-dominant late-onset form of the disease (ADO) was anticipated, with a 50% chance of inheritance in the fetus.

On endocrinology advice, combined vitamin D and calcium supplementation (Calcichew D3 Forte calcium 1.25 g, vitamin D₃ 400IU [Shire Pharmaceuticals Ireland Ltd, Dublin, Ireland]) was commenced together with regular checks of serum calcium levels with renal and bone profiles. Supplemental calcium or vitamin D is usually not recommended in the normal course of ADO management, as both have been reported to cause symptomatic hypercalcaemia; however, it was assumed in this case that greater fetal demands might lead to increased requirements. Prepregnancy dental care was good and oral hygiene was encouraged. Physiotherapy was commenced in the second trimester, and pelvic girdle pain managed initially with simple analgesia. These symptoms necessitated the patient giving up work after 20 weeks of gestation. Fetal anomaly ultrasound at 21 weeks of gestation was normal and regular fetal growth scans were performed from 28 weeks onwards.

The patient was admitted at 27⁺⁶ weeks gestation, when she presented with worsening back pain, as well as severe new-onset left hip and leg pain, associated with paraesthesia and weakness. Serum markers of inflammation (e.g. C-reactive protein) were not elevated. An urgent magnetic resonance imaging of spine, pelvis and femur showed no evidence of new fractures, and no signs of dysplasia, osteoarthritis or osteomyelitis. Physiotherapy was continued, together with non-steroidal anti-inflammatory medication, and opioid analgesia for breakthrough pain. However, due to poor pain control and decreasing mobility, the pain specialist team decided to perform a trigger point injection to the left lower sacrum at 29⁺¹ weeks (without X-ray screening). This allowed for discharge on simple analgesia, with walking aids for mobility at home, and ongoing close outpatient surveillance.

At 36⁺⁵ weeks poor pain control necessitated repeat admission. The patient was now relatively immobile and regular opioid analgesia was used to manage constant pain. Fetal lung maturity was accelerated with a course of intramuscular dexamethasone and the decision for delivery was made in consultation with neonatology and anaesthetic teams. As very limited hip movement precluded vaginal delivery, the mode of delivery was determined to be caesarean section.

The patient was delivered by caesarean section under uncomplicated spinal anaesthesia at 37⁺¹ weeks of gestation. A 3200 g male infant was delivered with Apgar scores of 9 at one minute and 10 at five minutes. The newborn was initially observed in the Special Care Baby Unit for persistently high lactate levels and transient tachypnoea, but was later discharged in excellent condition. The patient was discharged home on day 6 after delivery, with reducing demands for analgesia and improving mobility. She had weekly physiotherapy for three months postnatally, but returned to good health and normal mobility by six months postpartum.

Formal genetic counselling was undertaken during the pregnancy and mutation screening was performed. Results of genetic testing postnatally confirmed a mutation in *CLCN7* and therefore the suspected diagnosis of osteopetrosis type II

(ADO) in our patient. Her son was later found not to have inherited the mutation.

DISCUSSION

Osteopetrosis is a rare disorder, and there is little information available on other patients with this condition, and none who had a pregnancy. The published literature largely focuses on the severe infantile forms of the disease and the only relevant adult case report dates from 1938.⁸ This describes a 26-year-old multiparous woman who presented with exhaustion in early pregnancy and was found to be anaemic. Radiological investigation showed generalized osteopetrosis and termination of pregnancy was advised.⁸

The so-called benign or late-onset form of osteopetrosis (ADO) usually manifests in late childhood or early adolescence, and is most commonly diagnosed radiologically at age 5–6 years, just as in this case. Between 80% and 90% of individuals with definite radiological signs develop clinical symptoms. The main complications affect the skeleton, and include fractures, scoliosis, osteomyelitis or hip osteoarthritis.^{2–5} Testing the BB-isoenzyme of creatine kinase and tartrate-resistant acid phosphatase can help to identify individuals who do not have diagnostic radiological findings.³ Both enzymes are reported as biological markers of the adult-onset of osteopetrosis, and their increased serum concentrations are thought to reflect increased osteoclast numbers.

While the patient described here was definitively diagnosed with osteopetrosis in childhood, genetic counselling and establishing the inheritance of the disease helped her understand the prospects for the infant. Of course, if the genetic basis of the disease in this patient were already known, prenatal diagnosis by chorionic villus sampling or amniocentesis would have been an option. Previous reports have discussed this, but only in the context of infantile osteopetrosis, where prenatal ultrasound has determined typical anomalies, e.g. skeletal hyperdensity, hydrocephalus or short long bones.^{9,10} Prenatal diagnosis of infantile osteopetrosis through chromosomal localization of the responsible gene and subsequent linkage analysis has also been reported.¹¹ However, apart from genes *LRP5* and *CLCN7* determining type I and II of adult-onset osteopetrosis, there are a large number of undetermined genes involved in this condition and genetic testing is still at an early stage.^{2,3,6,7}

In the case of osteopetrosis presented, the patient did not experience any fractures during pregnancy. Her multiple previous fractures and osteosclerotic bone are presumed to be the reason for her later symptoms, exacerbated by the physical demands of pregnancy. The main difficulty in management was to find the right balance between good pain control and the effects of strong analgesia on the fetus. Early physiotherapy and involvement of both the anaesthetic team and pain specialist team was useful. Bone health was maintained with vitamin D and calcium supplementation, on the advice of endocrinologists, despite the usual advice to restrict calcium and vitamin D intake in this condition. Increasing bone pain and lack of mobility was managed with the help of physiotherapy, mobility aids and increasing levels of analgesia. A trigger point injection to the sacrum provided some relief and gained time to prolong the gestation. Delivery by caesarean section in this case was necessitated by pain and limited hip movement; in ADO generally there is also a theoretical risk of fractures in labour as well as an increased chance of cephalo-pelvic disproportion from a sclerotic

pelvis and scoliosis. Finally, a multidisciplinary approach involving specialists in endocrinology, orthopaedics, physiotherapy, anaesthetics, pain management, geneticists, as well as good communication between patient and physicians proved the key to a good outcome in the management of this rare condition.

DECLARATIONS

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