Case Report

Ultrasound diagnosis of bilateral cataracts in a fetus with possible cerebro-ocular congenital muscular dystrophy during the routine second trimester anomaly scan

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Abstract

The finding of bilateral congenital cataracts in the fetus is rare. We report bilateral congenital cataracts detected during the routine second trimester anomaly scan, which subsequently were found to be associated with other congenital anomalies and the parents opted for a termination of pregnancy. At post-mortem, Muscle–Eye Brain disease or Walker–Warburg Syndrome was considered likely, which are autosomal recessive congenital muscular dystrophy disorders associated with cerebral, cerebellar, muscle and eye anomalies. On ultrasound, bilateral cataracts appear as echogenic, solid areas within the fetal orbits. The examination of the fetal face and orbits plays an important role in confirming fetal well-being antenatally. We propose that it should become a routine part of the structural survey of fetal anatomy during the obstetric anomaly scan. This is especially important in pregnancies previously affected by fetal cataracts or pregnancies at risk of rare genetic syndromes.

Keywords: Congenital fetal cataracts, ultrasound, lenses, orbits, dystroglycanopathy, congenital muscular dystrophy

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Introduction

A cataract is defined as any opacity in the lens of the eye. The incidence of congenital cataracts in new-born babies ranges from 1 to 6 new-born infants out of 10,000 births.¹ Congenital cataracts can be isolated and between 8.3 and 25% are believed to be inherited. Congenital cataracts can be inherited in one of three ways: autosomal dominant, autosomal recessive or X-linked fashion, with autosomal dominant being the most frequent mode of inheritance with high penetrance.² Congenital cataracts are also associated with genetic syndromes, congenital infections, metabolic disorders and chromosomal abnormalities. A genetic cause is responsible for 30% of unilateral cataracts and 50% of bilateral cataracts.³ Antenatal diagnosis of fetal congenital cataracts was first reported in the literature in 1991.⁴ The fetal lens and eye can easily be examined during the 2nd trimester anomaly scan, allowing the opportunity to pick up several abnormalities affecting the fetal eye. The following report describes the antenatal detection of bilateral cataracts during the routine anomaly scan.

Background

The eye is a complex organ as it is composed of many different types of tissue and specialised cells, which take in

light, convert them into electrical signals and transmit them to the brain. With so many dedicated cells working in such an intricate system, it makes the eye susceptible to a wide range of diseases. Examining the fetal eye can therefore play a very important role in identifying systemic diseases. See Table 1 for previous cases of prenatal diagnosis of congenital cataract and their cause or associated diseases.⁵ Fetal orbits and lenses can be seen by ultrasound from 14 weeks.⁶ The fetal orbit appears as an echolucent area symmetrically placed on either side of the fetal nose. The fetal lens appears as a circular hyperechoic ring with an anechoic centre (see Figure 1). Fetal cataracts are seen by ultrasound as solid, echogenic discs or areas of echogenicity within an echolucent orbit.

Case report

A 34-year-old female, gravida 2, para 0, attended the Ultrasound Department at 20⁺⁶ weeks for her routine anomaly scan. Her obstetric history included a previous ectopic pregnancy which was successfully removed surgically at five weeks. Her current pregnancy had been uncomplicated with an unremarkable dating scan and a combined screening result for Down syndrome of 1:100,000. She was scanned on an Aloka (Wellingborough, UK) Alpha 10

Table 1 Previous cases of prenatal diagnosis of congenital cataract and their cause or associated disease⁵

Syndrome	Cases
Facio-cranio-osteosynostoses:	
• Apert syndrome	3
Cranio-facial malformation syndromes:	
• Smith-Lemli-Opitz syndrome	2
• Hallerman Streiff syndrome	3
• Rubinstein Taybi syndrome	2
Musculoskeletal conditions:	
• Chondrodysplasia punctata syndrome	2
• Walker-Warburg syndrome	3
• Roberts Syndrome	2
Chromosomal anomalies:	
• Trisomy 13	1
• Trisomy 18	1
• Trisomy 21	1
Cutaneo-dental disorders:	
• Nance-Horan syndrome	2
Metabolic disorders:	
• Zellweger syndrome	1
• Lowe's oculo-cerebro-renal syndrome ⁷	1
Infectious diseases:	
• Rubella	3
• Varicella	2
• CMV	2
Idiopathic ⁸	2

machine with a UST-9130 transabdominal probe (2.1–6 MHz). The scan demonstrated no obvious fetal abnormality, except for an isolated finding of bilateral, hyperechoic and opaque lenses suggestive of bilateral cataracts (see Figure 2). The patient and her partner had no history of cataracts in themselves or their family. The patient was referred to a tertiary fetal medicine centre, where follow-up scans confirmed isolated bilateral cataracts in a male fetus.

The patient was offered maternal viral serology, testing for Cytomegalovirus, Toxoplasmosis and Parvovirus B19 and a fetal MRI. The viral serology screen to test for congenital infections came back as normal. The parents were counselled that the prognosis was dependent on what the tests showed, but timely surgical treatment of isolated paediatric cataracts can help with visual rehabilitation in some cases, although amblyopia and glaucoma remain a risk.⁹

An MRI was carried out at 22 weeks and reported that there was normal brain development, normal orbits and normal optic nerves. The lenses were seen but the MRI scan could not exclude cataracts. Although the Down syndrome screen, viral screen and fetal MRI were reassuring, an amniocentesis for fetal karyotype was discussed, but the parents declined the procedure in view of the risk of miscarriage. Arrangements were made for a four weekly review to monitor growth and the appearance of the fetal lenses.

At 26⁺² weeks, the isolated bilateral cataracts were again noted, but the cerebellum now appeared hypoplastic with

the transcerebellar diameter measuring just below the 3rd centile, making a diagnosis of isolated non-syndromic cataracts unlikely. A rescan was suggested two weeks later to check fetal growth and the growth of the cerebellum.

The bilateral cataracts were again seen at 28⁺² weeks and the cerebellum still appeared hypoplastic, measuring below the 3rd centile, although the remaining fetal biometry showed adequate growth velocity. The cerebellum is one of the last brain structures to reach maturation and undergoes rapid changes in size and differentiation in the second half of gestation. The rapid growth is the result of important developmental processes that may be vulnerable to genetic issues.¹⁰ Therefore, a second fetal MRI was requested as the brain structures were more fully developed. The repeat MRI was carried out at 30⁺³ weeks, which unfortunately reported that there had been poor development of the hind brain and hypoplasia of the cerebellum. There was abnormal cortical folding of the brain and the optical lenses appeared reduced in size. At this point the parents were further counselled regarding the option of an amniocentesis. However, it was felt that the severity of the MRI findings were such that their decision on continuation of the pregnancy would not be affected by the karyotype result.

In view of the late gestation and the severity of the ultrasound and MRI findings, a multidisciplinary meeting (MDT) of the various teams involved in the case (obstetricians, clinical geneticist, ultrasonographer, consultant neuroradiologist) was set up to discuss the prognosis and the options of management, including whether the findings fulfilled the criteria for offering a termination of pregnancy under Clause E. Following this MDT meeting the patient was referred for genetic advice and told that the MRI findings were highly suggestive of a congenital infection, a chromosomal problem or possibly a rare genetic syndrome. Possible genetic syndromes included Muscle-Eye Brain disease, due to the cerebral, cerebellar and eye anomalies or Lowe Syndrome, which is associated with brain anomalies and bilateral cataracts and is seen almost exclusively in male fetuses. There was also the risk that the fetus could have a high risk of blindness and a high risk of severe neurological handicap.

Following this counselling and further consideration, the parents requested a termination of pregnancy and a feticide, which was agreed to under Clause E and performed at 30⁺⁶ weeks with subsequent induction of labour. A detailed post-mortem was carried out and revealed a male fetus with a small brain of 26–27 week size. The eyes had a white pupil glare consistent with congenital cataracts. There was a small cerebellum with fusion of the cerebellar hemispheres, as well as hypotrophic skeletal muscles. The full karyotype was normal. DNA was stored from the baby for further genetic testing. The post-mortem was suggestive of a cerebro-ocular muscular dystrophy such as Muscle-Eye Brain disease or Walker-Warburg Syndrome caused by secondary dystroglycanopathy.

Cerebro-ocular muscular dystrophy

Cerebro-ocular muscular dystrophy forms a small group of muscle diseases and is caused by dystroglycanopathy.

Figure 1 Normal fetal orbits with normal lenses appearing as circular, hyperechoic rings with an anechoic centre, as seen at the anomaly scan

Figure 2 Ultrasonic views of the fetal eye at 20⁺⁶ weeks showing the congenital cataract as a solid, echogenic disc (see arrows)

Dystroglycanopathies are an autosomal recessive condition, so both parents must be carriers for the child to be affected. The carriers will have no symptoms and the chance of their child being affected is one in four. Non-affected siblings have a two in three chance of being a carrier.

A dystroglycan is a protein. Alpha-dystroglycan provides structural integrity in muscle tissues, the brain and the neural retina. Dystroglycanopathy occurs when the alpha-dystroglycan does not undergo glycosylation, an enzymatic process that attaches glycans to proteins. Glycans serve a variety of structural and functional roles in membranes and secreted proteins. Six genes have been identified in the glycosylation of the alpha-dystroglycan: POMT1, POMT2, POMGnT1, FKR1, Fukutin and LARGE.¹¹ If any of these genes are defective in the glycosylation process of the alpha-dystroglycan then dystroglycanopathy occurs, resulting in conditions such as Muscle-Eye-Brain disease and Walker-Warburg Syndrome. Currently,

only 50% of dystroglycanopathy patients can be explained with known genes and can be provided with a genetic diagnosis. In this instance, a definite diagnosis could not be made as the patient did not have any pathogenic mutation in the identified genes. On a research basis, the patient had subsequent testing of three further recently identified genes: ISPD, GMPD and B3GALNT2 but they also proved negative for any pathogenic mutation. Further testing on the stored fetal DNA is planned as new genes associated with the dystroglycanopathy are identified. Research suggests that there are at least five more candidate genes that still remain unidentified. At present, the only testing available to this patient in a future pregnancy is to look for fetal cataracts from 14 weeks of pregnancy and to have serial ultrasound scans and MRI measuring cerebellum development.

Muscle-Eye Brain disease and Walker-Warburg Syndrome have very similar clinical manifestations. They are both a rare form of autosomal recessive congenital

muscular dystrophy associated with brain and eye abnormalities. Both conditions present with generalised hypotonia, developmental delay and mental retardation. The children with Muscle-Eye Brain disease deteriorate dramatically after the age of five years and normally die between 6 and 16 years. Children with Walker-Warburg Syndrome often die before the age of three.

Discussion

The antenatal detection of bilateral fetal cataracts during the patient's anomaly scan was the first ultrasonographic sign of cerebro-ocular muscular dystrophy in the fetus at that time. The antenatal detection of fetal congenital cataracts can ensure appropriate prenatal assessment. If the congenital cataracts are isolated, then appropriate postnatal surgical management can contribute to an improvement in the child's visual development.⁹ As cataracts are also associated with rare genetic syndromes, congenital infections and metabolic disorders, the examination of the fetal face and orbits contribute towards an otherwise unlikely antenatal diagnosis of these conditions. Although there is no specific treatment for cerebro-ocular muscular dystrophy, an antenatal diagnosis can provide supportive and preventive management.

This case clearly demonstrates the complementary nature of ultrasound and MRI in the imaging of the fetal brain, especially when an abnormality is detected by antenatal ultrasound, but it is important to understand the limitations of both. Ultrasound appears to be better at displaying fluid space in the posterior fossa and for delineating arachnoid cysts. However, MRI displays advantages over ultrasound in terms of evaluating the cerebellum, the cerebellar vermis and the brainstem.^{12,13} MRI also has the advantage of not being as affected by maternal obesity compared to ultrasound.¹⁴ A disadvantage of MRI is that it can cause false-negatives if performed prior to 22 weeks due to the size and structural development of the brain, as demonstrated in this case report. Therefore, the type of imaging used needs to be based on the individual circumstances such as maternal body habitus, the fetal presentation, the type of abnormalities suspected and the local facilities for performing MRI.

Although the finding of bilateral fetal cataracts may be rare, looking at the fetal orbits and making an antenatal diagnosis has several important ramifications. There are far-reaching implications for the family if a child is born with significant congenital abnormalities. An antenatal ultrasound diagnosis allows parents to make an informed choice about whether to continue the pregnancy or make the necessary emotional adjustments to prepare for caring for a disabled child and the possibility that their child may have a short life expectancy.

Conclusion

The routine second-trimester anomaly scan is an integral part of obstetric care with set standards and guidance laid out by the NHS Fetal Anomaly Screening Programme (FASP) in 2010.¹⁵ The FASP guidelines recommend the

fetal lips are examined in the coronal view to exclude a cleft lip. By manoeuvring the ultrasound probe slightly cephalad, the fetal orbits and lenses can also be seen providing additional information about fetal well-being. Examining the fetal orbits and face should become an integral part of the obstetric anomaly scan. Indeed, The International Society of Ultrasound in Obstetrics and Gynaecology produced guidelines in 2010, which advocated that the minimum evaluation of the fetal face should include an attempt to visualise the upper lip, median facial profile, orbits, nose and nostrils.¹⁶ This is achievable within the recommended half hour slot for the obstetric anomaly scan and FASP should consider including the fetal orbits and face in their guidelines.

As ultrasound machines become more sophisticated and the technology advances, the improved resolution allows an increasing opportunity to see more and more during the obstetric anomaly scan. If it is possible to see important fetal anatomical structures that give vital clues about fetal well-being, then why ignore them? It is crucial that ultrasound practitioners are equipped with the skills to interpret the high resolution images, to be able to understand the implications of their findings and to be able to relate the information to the parents with effective and considered communication, so allowing parents to make informed choices about their pregnancy.

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Guarantor: AD.

Contributorship: AD researched the literature, obtained ultrasound images, obtained patient consent and drafted the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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