Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Dilated neonatal cisterna magna and Marfan syndrome

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Summary

The authors report the incidental finding of a dilated cisterna magna with an abnormal configuration to the falx in a newborn infant with Marfan syndrome who was recruited to a research study involving whole body MRI. To our knowledge, dilation of the cisterna magna has not previously been reported in patients with Marfan syndrome. Potential implications for antenatal diagnosis, the ethics of recruiting healthy volunteers for research and directions for future work are discussed.

BACKGROUND

Marfan syndrome is an autosomal dominant inherited condition of connective tissue that may affect the cardiovascular, skeletal, cutaneous, neurological, ocular and pulmonary systems. The condition displays variable expressivity in affected individuals. Mutations in the fibrillin gene (FBN1) which encodes the protein fibrillin-1

on chromosome 15q21.1 may be identified in 91% of cases but the diagnosis is generally based on a constellation of clinical findings.¹ Diagnosis in the newborn is difficult as the classical clinical features may not all be present. Several central nervous system problems have been associated with Marfan syndrome with dural ectasia occurring in approximately 40% of paediatric patients.² White

Figure 1 Antenatal ultrasound measurements at 21+2 weeks gestation

Figure 2 Cranial ultrasonography images and MR images

matter anomalies³ and epilepsy⁴ have also been described. To our knowledge, dilation of the cisterna magna has not previously been reported in patients with Marfan syndrome although it is mentioned as a clinical finding in a book chapter.⁵

CASE PRESENTATION

A male infant was born in good condition by forceps assisted delivery at 38+3 weeks gestation after induction of labour for maternal Marfan syndrome with worsening aortic regurgitation. Antenatal foetal scans including echocardiography were considered unremarkable though the head circumference and cisterna magna measurements were on a higher centile than other body measurements (figure 1). The birth weight was 3570 g (50th centile) and head circumference 37.5 cm (91–98th centile). The infant was thought to be well on general examination and was recruited following informed parental consent to a research study related to body composition involving whole body MRI. The sequences used in this study were not optimised for cerebral imaging but a large space in the posterior fossa was noted. Subsequent cranial ultrasound imaging and optimised brain MRI confirmed the presence of a dilated cisterna magna with a raised tentorium and split falx (figure 2). Cerebellar size and appearance were normal. Detailed clinical examination 3 weeks after birth revealed lax skin, long fingers and toes, an umbilical hernia and a tendency for the fingers to be held in flexion. At 2 months his head circumference was still between the 91st–98th centile and length was 58.5 cm (<75th centile). There was no palatal abnormality, scoliosis, pectus deformity, joint hypermobility or signs of raised intracranial pressure. At 5 and 12 months of age some contracture of the right wrist joint with limited degree of flexion, and hammer toes were noted. His neurodevelopment was normal. His post-natal echocardiogram showed normal aortic root dimensions, a normal mitral valve and loss of the sino-tubular junction. Ophthalmology assessment was unremarkable.

Orthopaedic opinion at 1 year of age confirmed ulnar deviation of the fingers of both hands with tight intrinsic muscles.

FAMILY HISTORY AND GENETIC ANALYSIS

In this family with four living affected members spanning three generations, a causative mutation has been found in the gene for fibrillin-1, located on chromosome 15q21.1. A deletion of a single nucleotide at position 3146 has been identified in our patient, his mother and a maternal aunt. This newly reported mutation in exon 25 leads to a premature stop codon at position 1087 in cbEGF-like domain #2, which is predicted to affect protein assembly.

DISCUSSION

This case demonstrates a dilated cisterna magna and split falx in a newborn infant with Marfan syndrome. A dilated cisterna magna is thought to be a normal variant in 0.4–1% of newborns but has also been described in association with aneuploidies.

It is not known, how common a finding this is in Marfan syndrome. Thus we suggest that antenatal ultrasonography of patients known to be at risk of Marfan syndrome should include an assessment of the cisterna magna dimensions. This would inform knowledge about this observation and may provide early evidence of the affected status of the foetus. At present, mutation analysis provides a definitive method of antenatal diagnosis. However it may be declined by the parents and in these instances the cisterna magna dimensions may be useful to the clinician.

A dilated cisterna magna, particularly when associated with a split falx is in the same category of abnormality as the dural ectasia seen in the lumbosacral region in up to 72% of adult patients with Marfan syndrome. Dural ectasia is now accepted as a major diagnostic criterion for Marfan syndrome but it is not identifiable antenatally. Whether the finding of a dilated cisterna magna parallels the incidence

of dural ectasia is unknown. This question might be clarified by incorporating brain imaging in the evaluation of Marfan patients with symptomatic dural ectasia.

This case also illustrates the complex ethical issues that arise in the recruitment of individuals thought healthy to research programs and the importance of the actions taken in the event of detecting an abnormality. It also raises the question of whether infants of parents known to have a heritable disorder should be recruited in to such studies. In this particular instance, prior to agreeing to enrolment, the parents received an information leaflet which highlighted that the MR scan was not for diagnostic purposes and that appropriate measures would be taken should there be an unexpected finding. The parents knew of the risk of Marfan syndrome but had opted not to go for early clinical diagnostic assessment. The finding from the research scan led to both a more extensive clinical examination of the infant that strongly suggested the diagnosis of Marfan syndrome, and also to repeat brain imaging and discussions about the implications of the findings. Although the parents appreciated the time spent with them it inevitably changed the events that occurred in the first postnatal weeks and led to expediting tests for the diagnosis of Marfan syndrome which they would otherwise have not undertaken at this stage.

Learning points

- Dilated cisterna magna may be a marker for Marfan syndrome that can be employed both antenatally and in the neonatal period to aid diagnosis. The potential implications of imaging undertaken for research studies require a prior consideration.

Competing interests None.

Patient consent Obtained.

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