Bruck Syndrome and Congenital Heart Disease: a novel association

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Introduction

- Bruck Syndrome (BS) is a rare autosomal recessive disease that is clinically characterized by features of both osteogenesis imperfecta and arthrogryposis multiplex congenita.
- It presents with multiple congenital joint contractures and bone fragility with various and/or recurrent fractures.
- Two genes are reported in this disease, FKBP10 and PLOD2, which are phenotypically indistinguishable and referred to as Bruck Syndrome Type I and II, respectively.
- Mutations in either one of these genes lead to malfunction in the crosslinking of bone collagen type I, secondary to altered telopeptide hydroxylation[1] which leads too the clinical signs we observe
- There are no reported cases of BS in the literature associated with any cardiac abnormalities

References

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Case Presentation

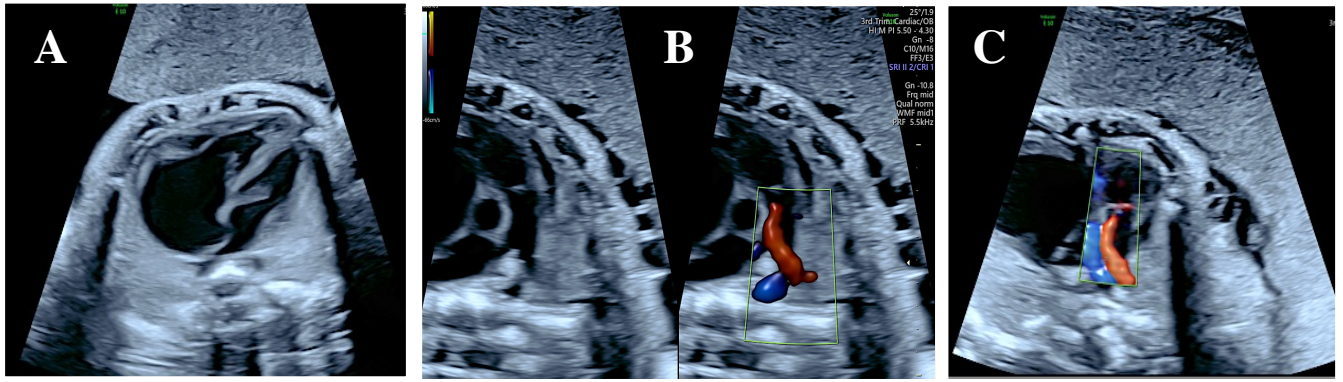
A 28 year old parous woman presented to our service at 35 weeks' gestation. The patient and her partner are second degree consanguineous with no significant personal or family history.

A first trimester morphology scan showed shorted long bones with bilateral fixed flexion of the elbow, wrist, and knee joints as well as bilateral talipes. An amniocentesis performed at this time genetically confirmed the diagnosis of Bruck Syndrome. Chromosomal microarray analysis testing reported a homozygous partial deletion of the PLOD2 and PLSCR4 genes. The partial deletion of PLOD2 would likely lead to a non-functional copy of the gene, whereas the clinical implications of a partial deletion in PLSCR4 remains unknown.

Serial scans continued to document severe long bone shortening and angulation. By mid gestation, bilateral fractures of the femur and humerus were diagnosed. Mid trimester cardiac screening had reported normal cardiac size and connections, however, at 35 weeks' gestation, new onset cardiac findings were detected, including significant cardiomegaly with an enlarged right heart secondary to severe tricuspid regurgitation, pulmonary valve insufficiency and a small arterial duct. There was no history of non-steroidal anti-inflammatory intake during the pregnancy.

Concerns for premature restriction of the ductus arteriosus lead to prompt delivery after a single 11.4mg dose of betamethasone. At 35+5 weeks, a live male baby was delivered by an en-caul caesarean section. At birth, limb fractures and contractures were clinically evident, and a cardiac echocardiogram confirmed tricuspid valve dysplasia with severe regurgitation, antegrade flow across the pulmonary valve and a restrictive arterial duct. Additional findings included an anterior mitral valve prolapse with mitral regurgitation and mild impairment of left ventricular systolic function.

The infant was managed therein by the neonatal intensive care team but despite treatment, passed away a short time after birth.



Discussion

- This is the first case of prenatal BS to be genetically confirmed by chromosomal microarray analysis of amniotic fluid.
- It is also the first documented case of BS with associated cardiac abnormalities.
- The PLOD2 gene encodes for lysyl hydroxylase 2, an enzyme that plays an important role in the crosslinking of collage type 1[2] which constitutes multiple parts of the cardiovascular system to provide myocardial structure and tensile integrity[3]. A defect in this gene would lead to myocardial dilation and decreased stiffness[4], highlighted in the findings of our case
- A limitation of this case is the unknown implications of the partial deletion of the PLSCR4 gene which has not been described in association with a human phenotype.
- This case highlights the important of ongoing evaluation throughout pregnancy for extra-skeletal abnormalities in foetuses diagnosed with BS given that the cardiac abnormality in out patient was not evident until the late third trimester.

Cardiac echocardiogram (35+4)

A. Enlarged right heart or atrium, the ventricle itself is actually not that big, due to the regurgitation of the tricuspid valve into the atrium.
B. Restricted ductus arteriosus. Red showing reversed flow through ductus.
C. Reversed flow (red) in pulmonary artery