Is chest wall deformity a serious issue? A rare case of TGFBR1 mutation in the paediatric population

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INTRODUCTION
Mutations in the genes encoding transforming growth factor β receptors 1 and 2 (TGFBR1 and TGFBR2) have recently been found in association with a continuum of clinical features.
Mild association – a presentation similar to that of Marfan’s syndrome.
Severe association – a complex phenotype in which aortic dissection or rupture commonly occurs in childhood and at aortic diameters, that ordinarily would not be predictive of these events. Classified as the Loeys–Dietz syndrome.
Is chest wall asymmetry a serious issue? A study of 71 patients with Loeys-Dietz – 9% died from aneurysm rupture or dissection with aortic diameters of less than 4.5cm and as early as 6 months of age.
Genetic variants of unknown clinical significance - how should they be managed?

CASE
History: 3-year old girl seen in general paediatric clinic with 5 months history of worsening chest wall deformity.
Examination: Asymmetrical pectus deformity. Spinal asymmetry and soft systolic murmur at the lower left sternal edge.

INVESTIGATION
Chest x-ray: Grossly enlarged and distorted cardiac/mediastinal silhouette.
Echocardiogram: Massive ascending aortic root dilatation (5.5cm) with significant aortic regurgitation.
MRI whole body angiogram: Massively dilated aortic root and ascending aorta to the proximal arch, hugely tortuous and ectatic cerebral vessels, diffuse marked dural ectasia, asymmetrical pectus deformity and a diaphragmatic morgagni hernia in the lower right hemi thorax.
Genetic analysis: Heterozygous missense variant of unknown clinical significance in exon 3 of TGFBR1 gene. The first heterozygous missense variant of its kind in the paediatric population for which its clinical significance remains unknown.

TREATMENT
As risk of dissection, a Bentall procedure was performed.
Family screening - Father has a dilated proximal ascending aorta.

LEARNING POINTS
Chest wall deformity should prompt clinicians to expedite investigations for aortic root dilatation/aneurysm and connective tissue disorders.
The continuum of clinical features of these genetic associations emphasises the importance of early recognition of the phenotype, prophylactic intervention and meticulous surveillance of the distal aorta and vascular tree for optimal management.
A genetic variant of uncertain significance (VUS) should not be used in clinical decision making. Efforts to resolve the classification of the variant as pathogenic or benign should be undertaken with good working relationships with clinical geneticists.
A VUS is difficult for patients and parents to understand and may also cause psychological distress. The importance of careful clinical and molecular characterisation to identify patients and families at risk cannot be overemphasised. This allows the use of a structured approach to intervention, informed counselling regarding the risk of recurrence, concerns related to pregnancy, and guidelines for clinical management.

Abstract P705 Figure. Case Photography and Imaging