Prenatal and postnatal echocardiographic manifestations of early-onset Marfan syndrome: a case report

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Abstract

Early-onset Marfan syndrome (eoMFS) is a rare subset of Marfan syndrome with varying phenotypic expression that occurs in the neonatal and infantile periods. eoMFS has a poor prognosis associated with high rates of mortality. Most newborn eoMFS patients present early onset heart failure that is resistant to treatment. This study presents a case of eoMFS.

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Running title: Echocardiographic manifestations of eoMFS

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Conflict of interest The authors declare that they have no competing interests.

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Abstract: Early-onset Marfan syndrome (eoMFS) is a rare subset of Marfan syndrome with varying phenotypic expression that occurs in the neonatal and infantile periods. eoMFS has a poor prognosis associated with high rates of mortality. Most newborn eoMFS patients present early onset heart failure that is resistant to treatment. This study presents a case of eoMFS.

Keywords: Marfan syndrome, Early-onset, Echocardiography, Gene

Case presentation

A 30-year-old woman (gravida 1, para 0) with no relevant personal or family medical history and no exposure to any known teratogen was referred to our department for fetal heart screening because of mild fetal tricuspid regurgitation at 24^{+6} weeks of gestation. Fetal echocardiography (Figure 1) at 26^{+1}weeks of gestation showed the fetal heart was normal (the aortic root was approximately 5.1 mm in diameter, Z score -0.29, and the main pulmonary artery was approximately 5.9 mm in diameter, Z score -0.21). Gene chip microarray analysis was performed at 26^{+5}weeks of gestation, and no abnormal chromosome number or pathogenic copy number variation was found. The child was female and born at 38 weeks. Neonatal echocardiography showed mild tricuspid regurgitation and aortic regurgitation at two days after birth. Regular child health care was planned. However, at three months after birth the aortic sinus was dilated (approximately 20 mm in diameter, Z score 6.1) and mild tricuspid regurgitation was observed. At one year and two months old, physical examination found a prominent forehead, sunken eyes, high palate, slender fingers and pectus carinatum. Cardiac auscultation revealed grade III systolic murmurs in the apical area and the third and fourth intercostal areas. Echocardiography (Figure 2) showed cardiomegaly and continuation of dilated aortic sinus (approximately 28 mm in diameter, Z score 7.1). The mitral and tricuspid valve leaflets were thickened, elongated and billowing toward the atrium during systole, complicated with moderate to severe and moderate regurgitation, respectively. According to the echocardiographic findings and physical signs, the diagnosis of Marfan syndrome was considered. Venous blood of the child and her parents were collected for whole-genome sequencing. The child had a single gene mutation in the chromosome 15 gene, fibrillin 1 (*FBN1*), at exon 25:c.3038G>T (p.Gly1013Val). The mutation was not found in the parents. Based on the child's physical signs, cardiac manifestations, and genetic mutation, the final diagnosis of early-onset Marfan syndrome was made.

Discussion

eoMFS is a rare and severe subtype of MFS. The eoMFS phenotype may be expressed in antenatal, neonatal, or infancy periods. However, the definition of eoMFS is controversial. Some authors suggest it to be the most serious subtype diagnosed in the perinatal period (1), while others suggest naming this form of MFS as infant MFS (2). Furthermore, most authors do not distinguish between eoMFS and neonatal MFS (nMFS). Hennekam (3) proposed that nMFS should be strictly applied to neonatal patients with severe mitral and/or tricuspid insufficiency and congenital pulmonary emphysema to indicate that it is a specific and severe form of MFS. In summary, eoMFS is more broadly defined than nMFS. The case presented here is more appropriately defined as eoMFS.

eoMFS is not easily diagnosed prenatally, even when ultrasound findings are present, because these are usually ambiguous and of late presentation. A systematic review by Veiga-Fernandez et al. of 39 articles gathering data from 54 cases, showed 34.54% of cases had prenatal ultrasound anomalies that helped raise the prenatal suspicion of eoMFS, while 65.45% were diagnosed in the postnatal period, without prenatal ultrasound findings (4). The most common prenatal findings were atrioventricular valvular prolapse and regurgitation. The next most common finding was cardiomegaly, followed by dilation of the great vessels. Among the cases with postnatal diagnosis, the most frequent cardiac ultrasound findings were pulmonary and aortic dilatation. The next most common findings were atrioventricular valvular prolapse and regurgitation. Cardiomegaly was the final cardiac manifestation. In our case, cardiac involvement of this patient appeared early and progressed rapidly. The main manifestations were aortic sinus dilation and atrioventricular valvular prolapse, which are consistent with the reported characteristics of eoMFS.

MFS is generally an autosomal dominant disorder with variable expressivity caused by mutations in *FBN1* . Approximately 75% of classic MFS cases are hereditary, while eoMFS is mainly sporadic (5). Varied changes in protein domains caused by these point mutations lead to diverse clinical phenotypes. Mutations in exons 24 to 32 are closely related to nMFS or eoMFS (6). Exons 24 to 32 are located in the center of the cbEGF domain and play an important role in the distribution and stability of microfibers (7). In our case, the *FBN1* mutation was located in exon 25. The mutation caused the glycine at position 1013 to be replaced by valine, which has a devastating effect on the formation of microfibrils.

Cardiovascular involvement appears early in children with eoMFS and their prognosis is poor. Echocar-

diography is of great significance for the diagnosis of eoMFS. For children with dilated aortic sinuses and atrioventricular regurgitation, the possibility of eoMFS should be considered. Early diagnosis, close follow-up, and timely treatment have a positive effect on improving the prognosis and quality of life of patients.

Figure legends

Figure 1 Echocardiographic manifestations at 26^{+1} weeks of gestation. (A) The size of the fetal heart was normal. (B) The aortic root was normal in diameter. (C) The main pulmonary artery was normal in diameter.

Figure 2 Echocardiographic manifestations at the age of one year and two months. (A, B) Aortic sinus dilation. (C) Mitral valve leaflets were thickened and elongated, and prolapsed toward the atrium during ventricular systole (arrow). (D) Tricuspid valve leaflets were thickened and elongated, and prolapsed toward the atrium during ventricular systole (arrow). (E) Moderate tricuspid regurgitation. (F) Moderate to severe mitral regurgitation.

List of abbreviations: AO, aortic root; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; PA, pulmonary artery

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