Cardiology in the Young

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Myxomatous degeneration of cardiac valves in a fetus with 6q25.1 (TAB2) deletion

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Brief Report

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Abstract

Myxomatous degeneration of one or more cardiac valves has been reported in trisomy 18, Noonan, Marfan, and Ehlers-Danlos syndromes. 6q25.1 (TAB2) deletion is one of the notable causes for myxomatous degeneration of cardiac valves. Whole exome sequencing must be considered in these subsets of cases for effective prenatal counselling. A 23-week fetus presented with cardiomegaly, redundant myxomatous tricuspid, mitral valve leaflets, thickened pulmonary valve, and bicuspid aortic valves detected to have 6q25.1 (TAB2) deletion was presented with literature review.

TGF-beta-activated kinase 1/MAP3K7-binding protein 2 (TAB 2 gene) deletion cause cardiac, especially valvular abnormalities and extracardiac abnormalities (distinctive facial features hypotonia, growth abnormalities, developmental delay, and connective tissue abnormalities). The described facial features include frontal bossing, dental problems, ptosis narrow palpebral fissures, and hypertelorism.[1–5] To best of my knowledge, only couple of cases in fetal literature has been reported so far.[2,9]

Case report

A 23-year-old primigravida was referred at 23 weeks gestation for fetal cardiac evaluation in view of cardiomegaly in routine obstetric scan. Four-chamber view showed cardiomegaly with thickened redundant myxomatous tricuspid and mitral valve leaflets. There was significant mitral and tricuspid valve prolapse with moderate tricuspid and mitral valve regurgitation. (Fig. 1a, b; Videoclip 1 and 2) Three-vessel view showed thickened right pulmonary artery. (Fig. 1c) Right ventricular outflow tract view showed thickened pulmonary valve (Fig. 1d, e) and bicuspid aortic valves (fusion of left and non-coronary leaflets) (Fig. 1f). High short-axis basal view of heart during diastole (Fig. 1g) and systole (Fig. 1h; Videoclip 3) showed densely thickened myxomatous tricuspid (arrow) and mitral valve leaflets (bold arrow). Invasive tests ruled out karyotype and 22q11 abnormalities. Whole exome sequencing detected a 471.5-kb deletion in the chromosome 6q25.1 (TAB2 gene). Considering the overall long-term outcome, the parents opted for termination of pregnancy. Parental whole exome sequencing and fetal autopsy were denied.

Discussion

The gene TAB2 [TGF-beta-activated kinase 1/MAP3K7-binding protein 2] mediates the activation of TAK1 in the IL-1 signal transduction pathway. TAB2 haploinsufficiency was associated with CHD.[1] Up-regulation of TGF-β expression is thought to have a role in mitral valve degeneration. Variable degrees of heart defects involving the valves, outflow tract, and septum have been reported in the literature. Polyvalvular dysplasia has been reported frequently in 6q25.1 (TAB2) deletion apart from trisomy 18, Noonan, Marfan, and Ehlers-Danlos syndromes.[2] A detailed literature search of various cardiac and extracardiac features of 6q25.1 (TAB2) deletion has been presented in Table 1.[2-9]

Conclusion

6q25.1 (TAB2) deletion is one of the notable causes for myxomatous degeneration of cardiac valves. Whole exome sequencing must be considered in these subsets of cases for effective prenatal counselling.

Table 1. Summary of previously published reports of 6q25.1 (TAB2) microdeletion syndrome.

Literature	Clinical features
Weiss et al.[2]	**Proband:** Fetus at 19 weeks gestation: tetralogy of Fallot, pulmonary atresia with severe myxomatous mitral, and tricuspid valve with prolapse.
	Proband's mother: Bicuspid aortic valve, myxomatous mitral and tricuspid valve prolapse, and ventricular septal defect.
	Maternal grandmother: Myxomatous prolapse mitral valve and supraventricular tachycardia. Her first pregnancy resulted in still birth, autopsy revealed bicuspid aortic valve, aortic stenosis, and hydrops fetalis.
	Proband's father has a family history of thoracic aneurysms and aortic dissection.
Cheng et al.[3,4]	**Cardiac findings:** Aortic stenosis/dilatation, atrial septal defect, bicuspid aortic valve, myxomatous mitral and tricuspid valve, pulmonary stenosis, overriding of aorta, patent ductus arteriosus, ventricular septal defect, hypoplastic left heart syndrome, and cardiomyopathy.
	Extracardiac findings: Growth restriction, hypotonia, developmental delay, intellectual disability, frontal bossing, short narrow palpebral fissures, retrognathia, and connective tissue abnormalities.
Woods et al.[5]	Newly identified features above the existing literature includes feeding difficulties, sleep problems, visual problems, and genitourinary abnormalities.
Engwerda et al.[6]	Mitral valve disease, cardiomyopathy, and distinct phenotype overlapping with Noonan syndrome.
Deng et al.[7]	Fetal scans at 24 weeks showed short legs. Postnatal echocardiography showed mitral valve prolapse with mild regurgitation
Salpietro et al.[8]	Fetal scans at 34 weeks showed intrauterine growth restriction. Postnatal findings – moderate perimembranous ventricular septal defect, mild mitral and aortic regurgitation, psychomotor delay, supraventricular tachycardia, generalised joint laxity with hyper-extensible thumbs, and fragile hyperelastic skin with marked increase in creases in the eyelids, neck, hands, and feet.
Gao et al.[9]	Fetal echocardiography at 34 weeks gestation showed ventricular septal defect, branch pulmonary artery stenosis, myxomatous mitral, and tricuspid valve prolapse

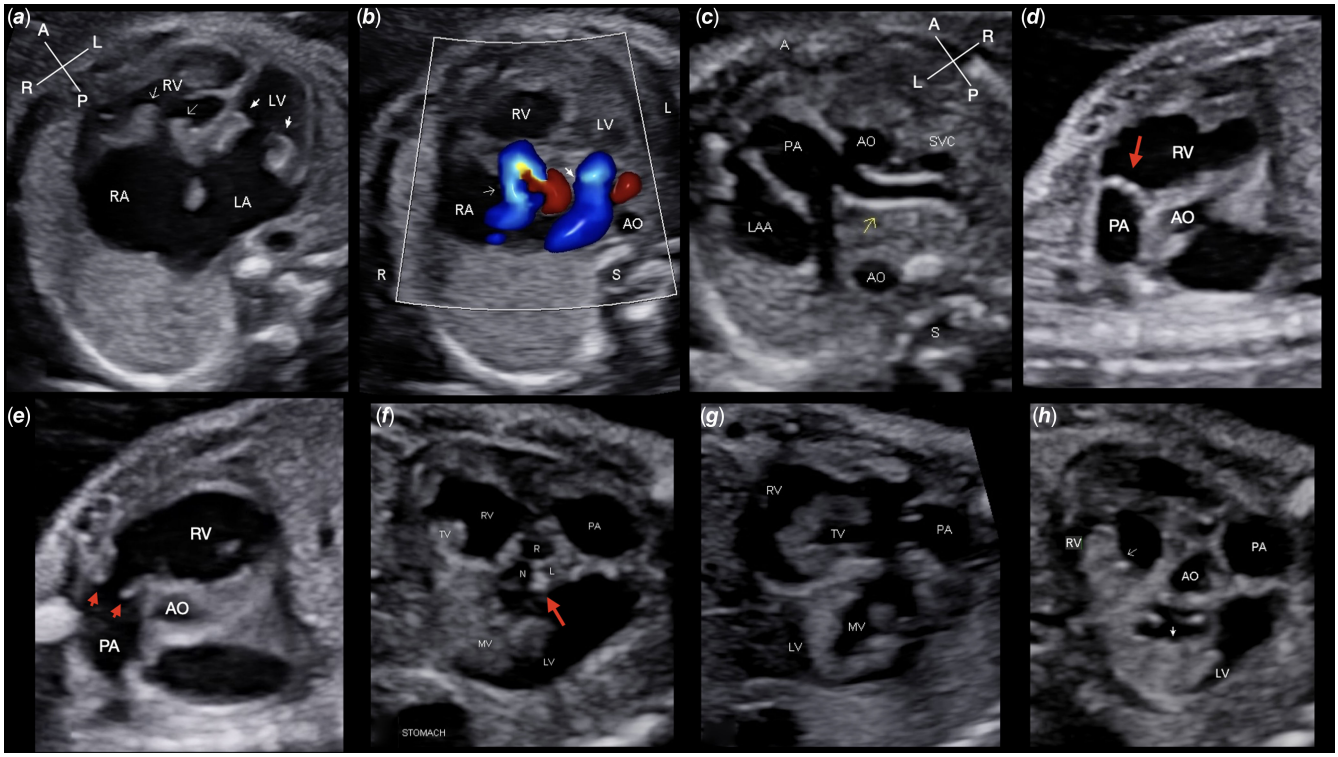

Figure 1. ***a*** – Grey scale 4-chamber view showing cardiomegaly with densely thickened redundant myxomatous tricuspid (arrows) and mitral valve leaflets (bold arrows). ***b*** – Four-chamber view colour Doppler showing moderate tricuspid (arrow) and mitral valve (bold arrow) regurgitation. ***c*** – Three-vessel view showing thickened right pulmonary artery. Right ventricular outflow tract view showing (***d***&***e***) thickened pulmonary (red arrow) and (***f***) bicuspid aortic valves (fusion of left and non-coronary leaflets) (red arrow). High short-axis basal view of heart during diastole (***g***) and systole (***h***) showing thickened redundant myxomatous tricuspid (arrow) and mitral valve leaflets (bold arrow).

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Informed consent. Informed consent was obtained as per our hospital policy.

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