Cardiology Lett. 2024;33(6):378–383
doi:10.4149/Cardiol_2024_6_4

Rare case presentation of thoracic aortic aneurysm and aortic dissection in adolescent

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Bobik L, Tittel P, Kardos M, Drangova E, Hulman M, Sojak V, Sabateen F, Kasicova K, Olejnik P, Zahorec M, Hrckova G, Hamidova O. **Rare case presentation of thoracic aortic aneurysm and aortic dissection in adolescent.** Cardiology Lett. 2024;33(6):378–383

Abstract. *Introduction:* Familial thoracic aortic aneurysm and aortic dissection (f/TAAD) is a genetic disease defined by disturbance in encoding the major proteins in the smooth muscle cells (SMC) contractile filaments of alpha-actin *ACTA2* and myosin heavy chain *MYH11*, in an autosomal dominant pattern. *MYH11* gene mutation is a rare cause of f/TAAD and is identified primarily in families with non-syndromic TAAD, inherited in association with patents ductus arteriosus (PDA). *Case report:* We present a 17-year-old girl with TAAD of ascending aorta and *MYH11* gene mutation, confirmed respectively. At the first year of age, the patient underwent PDA interventional transcatheter closure. Owing to suspicion of coarctation, recatheterization was performed at the age of 4 years, without confirmation. Afterwards she was followed up by a pediatric cardiologist. At the time of examination she was referred to consultation due to non-specific precordial feelings. Physical examination showed no signs of connective tissue abnormalities. Transthoracic echocardiography revealed severe dilation of ascending aorta with the presence of flap contour from sinotubular junction up to the ascending aorta and new onset of aortic regurgitation, and so dissection of ascending aorta was suspected. CTA was performed and confirmed the diagnosis of Standford A dissection, with the entry at the level of sino-tubular junction and re-entry at the level of ascending aorta before the epiaortic branches of the proximal aortic arch. The patient underwent surgical procedure with resection of the damaged part of aorta ascendens and implantation of tube graft, with a good postoperative course. Genetic analysis focused on genes associated with vasculopathies and connective tissue abnormalities was performed and a pathogenous variant of 4599+1G>A *MYH11* gene mutation was confirmed. There was no history of sudden cardiac death in the family, nor of other cardiovascular diseases. So far no other affected family members have been positively indicated in the pedigree: de novo mutation is probable. The patient is without any incident or complications to date; follow-up CTA scan is without progression. Postoperative repetitive magnetic resonance angiography of the central nervous system has revealed multiple changes due to previous microhemorrhagia, which are stable in observation, and the patient does not have any neurological deficit.

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Manuscript received 28 August 2024; accepted for publication 26 September 2024

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Conclusion: Very early presentation of ascending aorta aneurysm and dissection led to *MYH11* mutation confirmation in a non-syndromic TAAD/PDA phenotype patient. The risk from the progressive character of the disease had led to intense and regular follow-up of the patient, with the need for repetitive imaging of the other parts of aorta and branches and of the cerebral arteries owing to potential future occlusive vascular pathology. Potentionally early intervention must be performed. Fig. 11, Ref. 14, on-line full text (Free, PDF) www.cardiologyletters.sk
Keywords: TAAD – thoracic aortic aneurysm – aortic dissection – *MH11 gene* mutation

Thoracic aortic aneurysm and aortic dissection (TAAD) leading to acute ascending aortic dissection is a common cause of premature sudden cardiac death, especially within the context of defined monogenic syndromes, such as Marfan syndrome and Loeys-Dietz syndrome, called "syndromic TAAD" (1). Similar observations of isolated aortic aneurysm formation in family members of patients with BAV have been reported (2).

Up to 20% of the patients do not have an identified genetic syndrome and present with an isolated manifestation, so-called "non-syndromic TAAD" (3). These are typically inherited in an autosomal dominant manner, with the absence of a clear syndromic constellation. If the first degree relatives are similarly affected, they are termed "familial TAAD" (f/TAAD).

Case report

History: A 17-year-old girl with TAAD of ascending aorta, who underwent PDA interventional transcatheter closure at the first year of age. Owing to suspicion of coarctacion, recatheterization was performed at the age of 4 years, but it was not confirmed. Afterwards she was followed up and referred to consultation because of non-specific precordial feelings.

Physical examination at the time of evaluation revealed neither dysmorphic features reminiscent of connective tissue abnormalities, skin manifestations, nor other vascular involvement. No family history of sudden cardiac death or cardiovascular disease was present. Electrocardiogram was without specific changes.

Diagnostic Imaging

Transthoracic echocardiography (TTE)

This revealed severe dilation of ascending aorta (Z sc +5.3) with double intimal flap, new onset of moderate aortic regurgitation, and dissection of the ascending aorta was suspected (**Figure 1-4**).

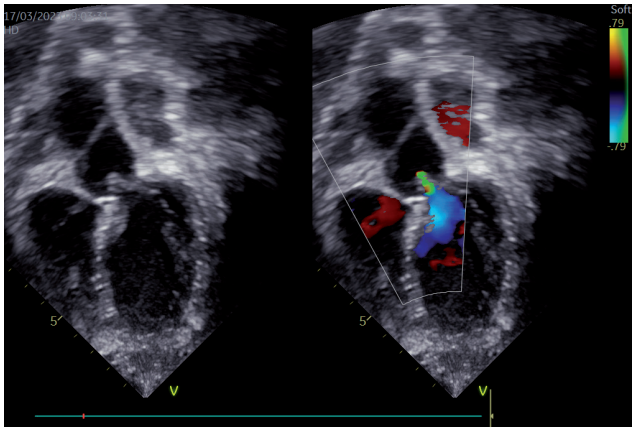

Figure 1 3 chamber view – aortic regurgitation and diagonal course of intimal flap in ascending aorta

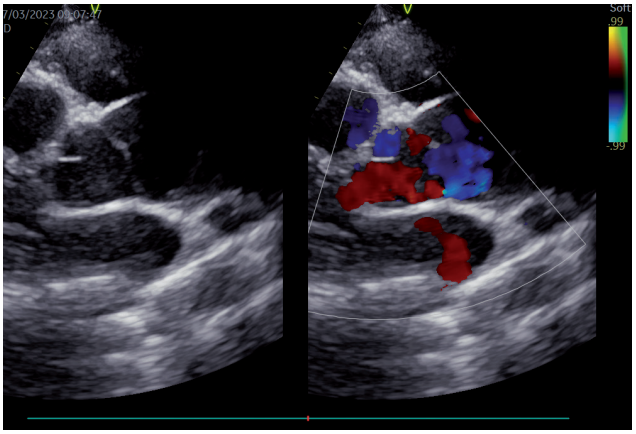

Figure 2 Parasternal long axis view – dilation of ascending aorta with entry level above right coronary sinus of Valsalva

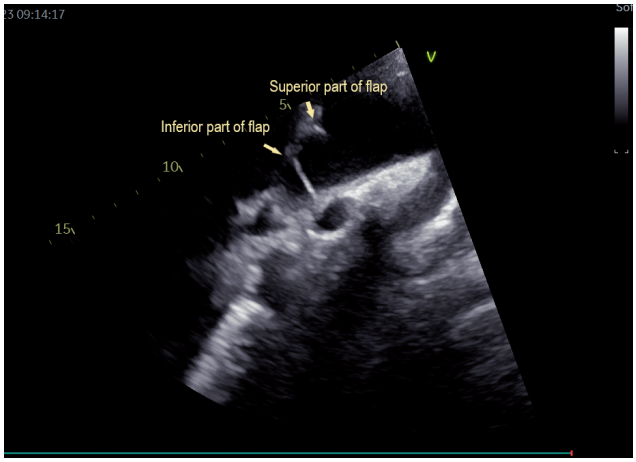

Figure 3 Suprasternal view of double intimal flap in ascending aorta

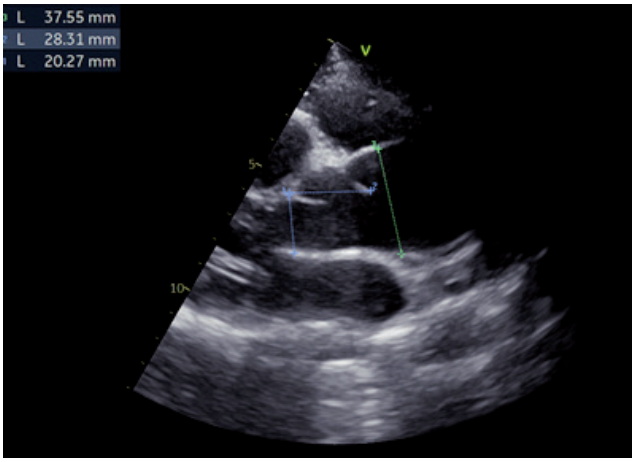

Figure 4 Parasternal long axis view dilation of ascending aorta Z +5.3

Computed Tomography Angiography (CTA)

CTA confirmed the suspected Standford A dissection with the entry at the level of sino-tubular junction and reentry at the level of ascending aorta proximal to epiaortic branches of the proximal aortic arch (**Figure 5**). Detailed 3D virtual reconstruction is shown in **Figure 6-9**.

Surgery and histopathology

Patient underwent surgical procedure with resection of the damaged part of aorta ascendens and implantation of tubegraft (Vascutek 24mm). Histopathological changes of tunica media with cystic medionecrosis and deposits of proteoglycans were present. Repetitive TTE and CTA showed kinking of the graft without any residual dilation, stenosis, obstruction, or intramural thrombi (**Figure 10-11**).

Genetic analysis

Genetic analysis focused on genes associated with vasculopathies and connective tissue abnormalities was performed, and pathogenous variant of *MYH11*

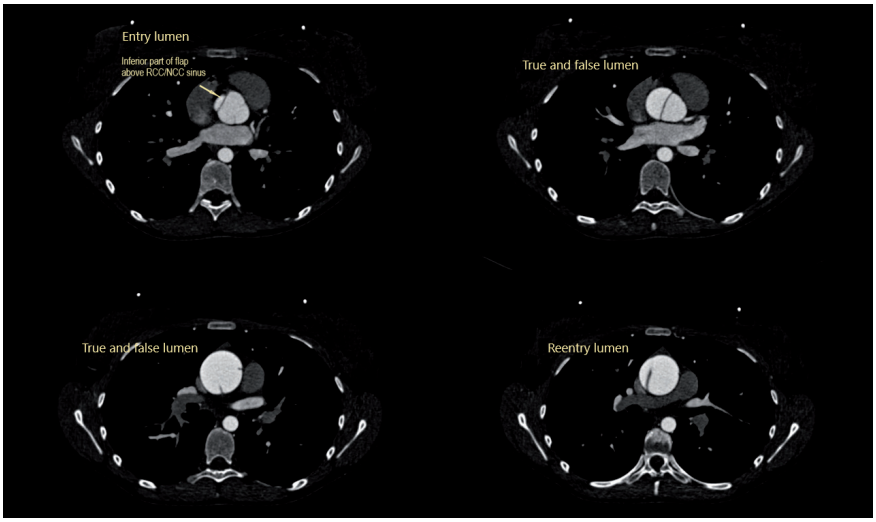

Figure 5 CTA – axial scan showing aneurysm dilation of ascending aorta with flap contour

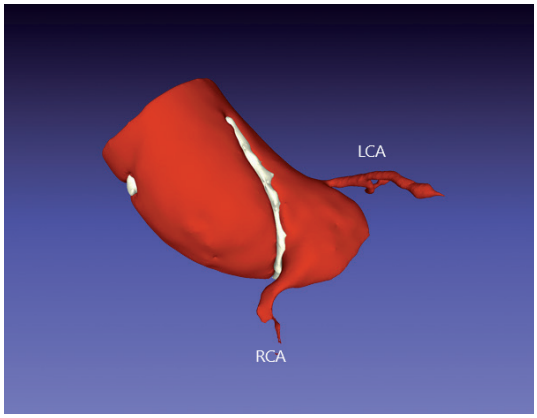

Figure 6 Right lateral view of ascending aorta aneurysm, flap above right and non-coronary sinus of Valsalva
RCA – right coronary artery, LCA – left coronary artery

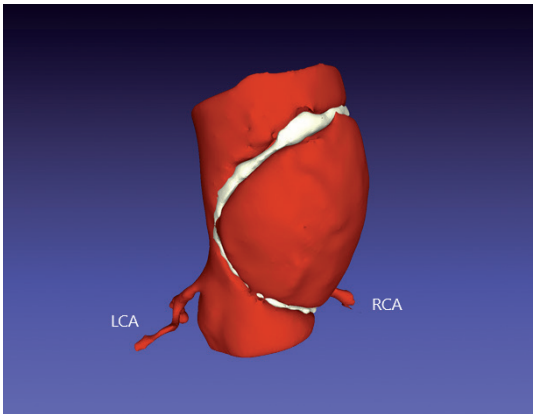

Figure 7 Posterolateral view of aneurysm and dilation of ascending aorta
RCA – right coronary artery, LCA – left coronary artery

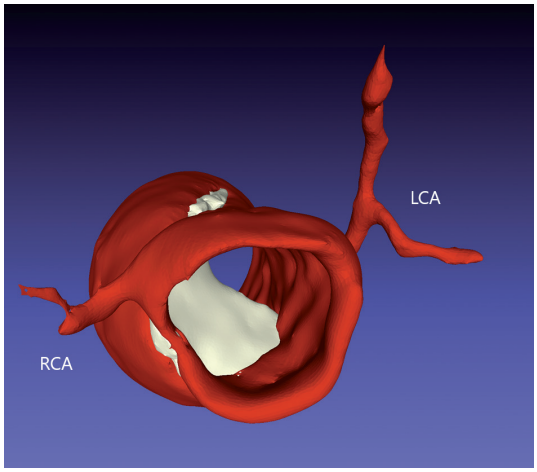

Figure 8 Inferior internal view – double spiral flap
RCA – right coronary artery, LCA – left coronary artery

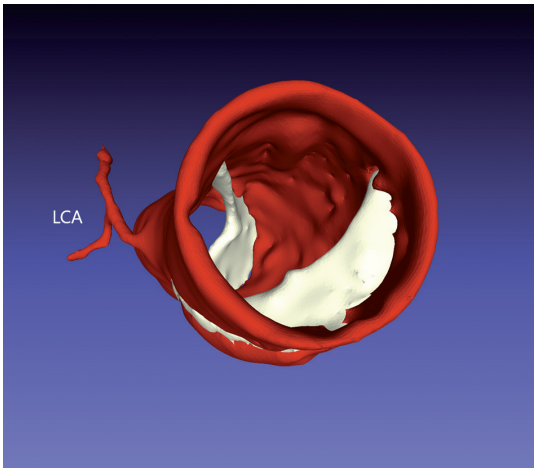

Figure 9 Superior left internal view of aortic flap
LCA – left coronary artery

4599+1G≥A associated with PDA was detected (*Twist Human Core Exome Kit Analysis*). No other affected family members were positively indicated in pedigree. Metabolic panel examination was negative.

Regular follow-up, imaging and pro-active searching of progression

Postoperative period and follow-up was without incident and complications. Follow-up CTA scan of aorta (2 and 9 months CTA post-op) demonstrated no progression to date, potentially with the need of early intervention in future. Magnetic resonance angiography (MRA) of central nervous system (10 and 16 months post-op) showed multiple changes infra- and supratentorially due to previous microhemorrhagia: they are stable in observation. The patient does not have any neurological deficit.

Discussion

Genetic contribution

The research into the genetic contribution of isolated TAAD has started in the last decade. To date changes have been found in genes encoding "Heritable thoracic aortic

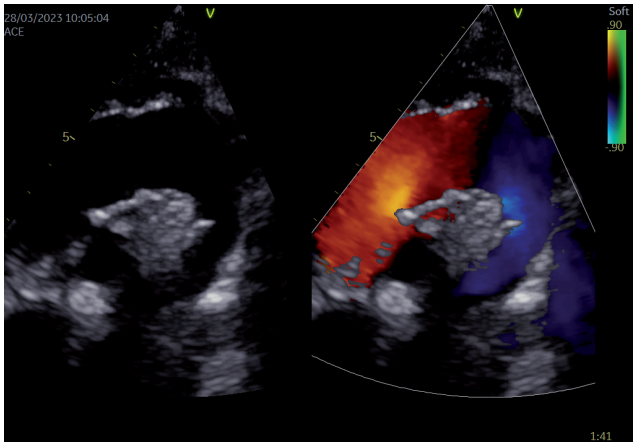

Figure 10 Postsurgical TTE – suprasternal view of laminar flow in tubegraft

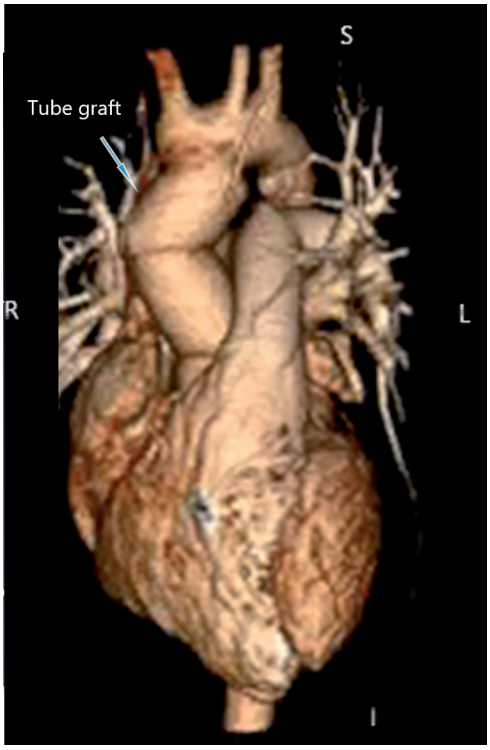

Figure 11 Follow-up CTA 3D model

disease genes – HTAD" (3, 4). These include extracellular matrix proteins – *FBN1*, *CP3A1*, proteins involved in transforming growth factor – TGFβ signaling *TGFBR1/2* (5), *SMAD3* gene (member of TGAβ pathway), which display a phenotype mainly characterized by ascending aortic aneurysm and dissection with early onset osteoarthritis (6), and proteins that build up the contractile apparatus of aortic smooth muscle cells (SMC) – *MYH11*, *ACTA2*, *MYLK* (5, 6, 7, 8). These novel gene defects encoding SMC specific isoforms are reported in the context of TAAD and counted in up to 10-16% of TAAD families.

ACTA2 – cytoskeletal protein actin α2 mutations are associated with aortic root dilation and a variety of cardiac – PDA, bicuspid aortic valve and extracardiac abnormalities. These include iris flocculi, liveto reticularis, cerebrovascular accident and stenosis of the aortic vasa vasorum, premature onset of coronary artery disease and stroke (extravascular traits). This mutation is the most common cause of f/TAAD identified to date (14%) (9).

MYLK (myosin light chain kinase) mutation involved in SMC or calmoduling binding properties of the protein, clinically leads to acute aortic dissection with minimal or no aortic enlargement prior to dissection.

MYH11 (myosin heavy chain protein 11) is a part of the myosin superfamily. SMC myosin is a hexameric complex composed of 2 myosin heavy chains – SM-MHC – encoded by *MYH11*, 2 essential and 2 regulatory light chains (RLCs). *MYH11* – specific contractible protein of SMC maintains structural integrity of the aortic wall, with disability of polymerization to form thick filaments and then interaction with actin in thin filaments. This leads in disturbances of contractility, lower aortic compliance and elastolysis as well as focal vascular SMC hyperplasia. Histopathological staining indicates hyperproliferation of SMC and the alteration of morphology – the presence of round-shaped cells instead of elongated cells. In vitro analysis of the consequences of the rare *MYH11* variant *R247C* with single lysin deletion led to decreased aortic contraction, in response to vascular injury, and significantly increased neointimal formation due to increased SMC proliferation (10, 11).

Zhu et al. have shown that *MYH11* gene mutation is associated with autosomal dominant type of inheritance, with dominant transmission in conjunction with PDA (12). *MYH11* gene mutation is connected to early onset of occlusive vascular disease and stenotic arteries in the vasa vasorum of the aorta and central nervous system. There have been identified in only a few familial cases associated with *L1264P (3791TC)* and *R1275L (3824GT) MYH11* gene mutation (13).

Renard et al. (4) reported a cohort of 110 non-syndromic TAAD patients (43 of f/TAAD), previously tested

negative for *FBN1/BR1-2* mutations and concluded that *MYH11* mutations are rare and causal to TAAD specific phenotype, typically identified in 1 patient associated with PDA, and *ACTA2* mutations identified in 22 patients (16%) of a cohort presenting fTAAD. They present that this is the fifth *MYH11* mutation reported to date, and confirm that *MYH11* mutations are rare and causal to this specific phenotype of TAAD associated with PDA. They have also published the hypothetical model of the pathogenetic mechanism of *MYH11* and *ACTA2* mutations.

Identification of *MYH11* mutations causing TAAD is very complicated, as very rare, nonsynonymous, variants occur in the population – 0.6% of the individual exomes in the Exome Rare Variant Database (14).

Conclusion

Non-syndromic chronic f/TAAD with very early presentation (retrospectively at the age of 13 years in our patient) is an extremely rare diagnosis, especially in children with negative family history: even more the *MYH11* gene mutation – *MYH11 4599+1G≥A* associated with PDA. Genetic family conselling is necessary in each case. So far no other affected family members have been indicated in pedigree, therefore de novo mutation is the most probable in our patient.

Regular follow-up and pro-active searching of progression to the other parts of aorta and vascular damages are needed. Repetitive CTA/MRA scan, potentionally with intervention (Total arch replacement, Frozen elephant trunk etc.) must be performed early enough. Regular MRA of central nervous system is also recommended.

I declare that there is no conflict of interest.

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