Přehledový článek | Review article

The journey of a patient with *ACTA2* mutation – literature review and case report

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SOUHRN

Postižení aorty představují významnou součást spektra kardiovaskulárních onemocnění. Mutace *ACTA2* je hlavní příčinou familiárního vzniku aneurysmat a disekce hrudní aorty, které se projevují dilatací nebo disekcí hrudní aorty jedinců bez systémové poruchy pojivové tkáně nebo příslušných syndromů. Gen *ACTA2* kóduje aktin, konkrétně α-aktin hladkého svalu, jenž je izoformou aktinu v hladkých svalech cév. Uvedená mutace vede ke vzniku řady postižení aorty, ale současně i k multisystémové dysfunkci hladkého svalu. Popisujeme případ pacienta s typickými klinickými nálezy odpovídajícími mutaci *ACTA2* a výsledek léčby po endovaskulárním a následném chirurgickém výkonu. Projevy a rozvoj klinických symptomů u našeho pacienta přesně odpovídají popisu onemocnění v literatuře.

Keywords:
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ABSTRACT

Aortic pathologies are a main part of the cardiovascular disease specter. *ACTA2* mutation is the main cause of familial thoracic aortic aneurysms and dissection, which is presented by dilation or dissection of the thoracic aorta in people, who do not have systemic or syndromic connective tissue disorder. The *ACTA2* gene encodes the specific α-smooth muscle actin, which is an isoform of vascular smooth muscle actin. This mutation mainly leads to aortic pathologies, but it also presents a multisystemic smooth muscle dysfunction. We present a patient with typical clinical findings, consistent with an *ACTA2* mutation and the treatment outcomes after consecutive endovascular and surgical interventions. The presentation and the evolution of the clinical symptoms of our patient closely follow the description of the disease in the literature.

Introduction

Cardiovascular diseases (CVD) are the leading cause of death worldwide, responsible for over 17 million deaths annually. Aortic pathologies are an important part of the CVD specter, because of their high mortality and morbidity rate. Approximately 20% of the aortic pathologies result from inherited disorders, most of them being syndromic connective-tissue diseases, like Marfan syndrome, Ehlers–Danlos syndrome, and Loeys–Dietz syndrome.[1] On the other hand, there is an autosomal dominant disorder, called familial thoracic aortic aneurysms and dissection, which is presented by dilation or dissection of the thoracic aorta in people, who do not have systemic or syndromic connective tissue disorder. According to the literature, 12% to 21% of the familial thoracic aortic aneurysms and dissections are caused by mutations in *ACTA2* gene.[2]

Review

Although the syndromic disorders and the familial thoracic aortic aneurysms and dissections lead to dilation and dissection of the aorta, there are important differences. According to Regalado et al., patients with *ACTA2* mutation suffer Type B aortic dissection less frequently, than Type A aortic dissection, but at younger age (median age – 27 years).[2] While the median age of aortic event in patients with *ACTA2* mutation is 34.2 years, the youngest individual reported is a 12-year-old female with homozygous missense mutation. There are slightly more male patients with *ACTA2* mutation and aortic dissection is detected in 62.1% of the male patients and in only 37.9% in the female group of patients.[2] Individuals with *ACTA2* mutation are often diagnosed on presentation with an aortic event, which is typica-

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lly acute aortic dissection at significantly younger ages, compared to patients with Marfan syndrome, often presenting with skeletal and ocular features.[3] Furthermore, Regalado et al. report that type B dissections are frequently complicated by aortic rupture and visceral and limb ischemia. Since, *ACTA2* encodes the smooth muscle-specific isoform of α-actin, the expected pathologies in patients with *ACTA2* mutations can involve every tissue and organ, containing the muscle-specific isoform of α-actin. Stating that, we can suspect multisystemic smooth muscle dysfunction, characterized by intestinal hypoperistalsis, pulmonary hypertension, fixed dilated pupils, cerebrovascular disease, and increased risk of earlier stroke incidence or coronary artery disease.[2] Actin is a multi-functional, most abundant protein in eukaryotic cells. There are three main actin isoforms, expressed by vertebrates. The three main isoforms – cardiac, skeletal, and smooth muscle, differ by only a few amino acids.[4] The *ACTA2* mutation consequences can be explained by the molecular structure of actin. Mutation in the amino acids – *Tyr135*, *Arg149*, and *Thr353* disturbs the integrity of the main hydrophobic sequence, where regulatory proteins and toxins bind.[5] The *ACTA2* gene encodes the specific α-smooth muscle actin (SMA) and it is an isoform of vascular smooth muscle actin. Motility and contraction are the main functions of the smooth muscle cells and these functions are maintained microfilament bundles where the α-SMA is located.[6] A missense mutation in the *ACTA2* gene accounts for the majority of the familial TAADs. Heterozygous mutations in *ACTA2* directly disrupts the ability of the arteries to stretch and results in significantly higher pressure, which leads to aneurysms and dissections.[7] Guo et al. analyzed aortic tissue from six individuals with *ACTA2* mutation and compared them to control aortas. They found that in the aortas from the individuals with *ACTA2* mutations there is increased proteoglycan accumulation, fragmentation, decreased number of smooth muscle cells, all findings typical for medial degeneration of the aorta. In some parts of the mutated aortas, there were an increased numbers of smooth muscle cells, lacking in structured orientation.[5] In order to prevent the serious vascular events, resulting from *ACTA2* mutation, timely recognition of the affected families is crucial, but unfortunately, the only alerting events in these families are findings of aortic dissection in probands.[8]

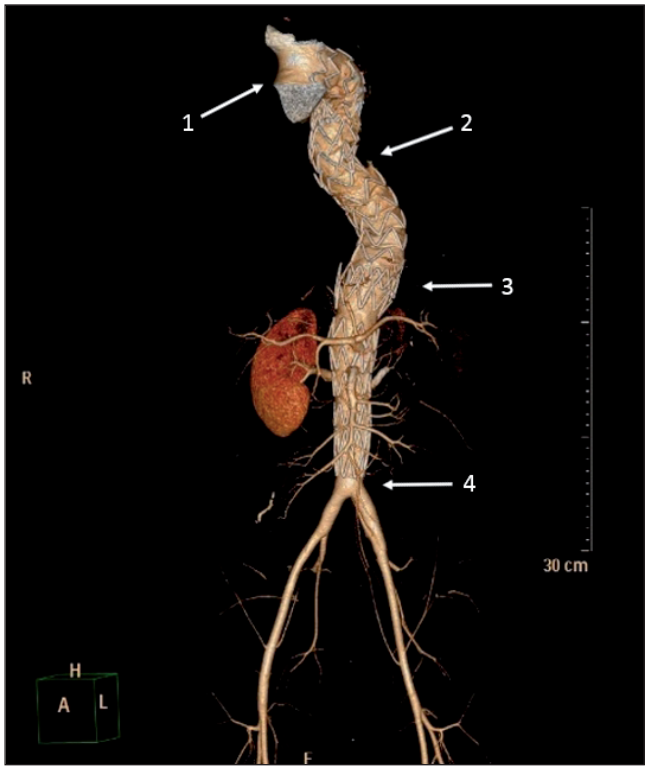

Fig. 1 – The most recent CT of the aorta, after consecutive endovascular and surgical interventions: 1 – Status post reimplantation of the aortic root and aortic valve replacement. 2 – Implanted stent-graft in the distal aortic arch, right after the ostium of the left common carotid artery. 3 – Two over lapping stent-grafts implanted in the thoracic aorta. 4 – Non covered dissection dedicated stent implanted in the thoracoabdominal aorta to the level of the bifurcation of the aorta, patent stents in the left renal artery and superior mesenteric artery, implanted through the cells of the aortic stent. No residual aortic dissection or aneurysm evident.

Case report

We describe a patient with clinical symptoms and progression typical for *ACTA-2* mutation. The patient who actually was then (2015) a 15-year-old child presented for the first time with sudden onset of severe back, chest, abdominal and left leg pain. The patient was well built (BMI = 24.59), with normal skin texture and no marfanoid features. He had a history of surgical correction of patent ductus arteriosus (PDA) at the age of 6 months and had no family history of connective tissue disorders. He led a normal and healthy lifestyle (no tobacco and alcohol use), but he had begun training more intensely, including weightlifting in the past month. Our patient was hemodynamically stable with weak and almost missing peripheral pulsations on the left femoral and popliteal artery. The patient had crescendo abdominal pain with reduced peristaltic sounds. The echocardiography upon administration revealed a slightly dilated ascending aorta and a mild aortic and tricuspid regurgitation. The admission CTA revealed a type B aortic dissection with semi-occlusive and occlusive compression of the true lumen of the superior mesenteric, left renal, and left iliac arteries causing life-threatening severe malperfusion syndrome. The origin of the intimal tear was just distal to the left subclavian artery (type B aortic dissection). The dissection reached the aortic bifurcation and penetrated the left common iliac artery. The right renal artery originated from the true lumen. The young age of the patient, the history of PDA and the complicated type B aortic dissection, without syndromic features and family history raised suspicion for an underlying *ACTA2* mutation, which later was confirmed through a genetic analysis. Our patient had *R258C* mutation, which is located in a helix on the backside of subdomain 4. R258C corresponds to R256 in the actin protein. This point mutation is the most prevalent cause of fTAAD, yet the

molecular mechanism by which it affects the actin function is unknown. In this critically ill patient, we performed a multistage endovascular treatment including stenting of the superior mesenteric artery, stenting of the left renal artery, stenting of the abdominal aorta, fenestration and balloon angioplasty of the left iliac artery and implantation of a stent-graft in the thoracic aorta. This case, to our knowledge, was the first successful endovascular treatment of type B AD in a child.[9] During a subsequent four-yeas follow-up, he developed an aneurysmal dilation of the thoracic aorta at the distal edge of the TEVAR endograft and a dilation of the ascending aorta. Complete isolation of the thoracic aneurysmal sac was achieved by the endovascular implantation of a second stent-graft (telescoped within the first). Due to the aneurysm of the ascending aorta and a severe aortic regurgitation, aortic root replacement and aortic valve repair was undertaken on a third stage. (Fig. 1) Interestingly enough, the patient was diagnosed with pulmonary hypertension, another symptom, associated with the *ACTA2* mutation. Six months after the open cardiac operation, our patient suffered a rupture of the appendix, which was treated successfully by timely surgical intervention. The ruptured appendix is a complication of the intestinal hypoperistalsis described in *ACTA-2* mutation. In addition, he has mydriasis, also described in *ACTA-2* mutation positive cases.

The presentation and the evolution of the clinical symptoms in our young patient, closely reminds the case described by Regalado et al.[2] We believe that our case, which shows the typical journey of a patient with *ACTA2* mutation and the successful treatment combining endovascular and surgical approaches will be of an interest and will contribute to the knowledge in the field.

Conclusion

ACTA-2 mutation is a significant genetic contributor to a variety of connective tissue disorders, the risk of which is led by the aortic complications. Timely endovascular and surgical treatment of these complications can save the patient's life, shown in our case during 6 years of strict follow-up and serial interventions.

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