

## GIRL WITH TAKAYASU ARTERITIS -PROGRESSIVE COURSE OF THE DISEASE AND MULTIPLE SURGICAL INTERVENTIONS

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Takayasu arteritis is a rare large-vessel vasculitis but it can be associated with high mortality rates in childhood. Granulomatous vasculitis usually affects the aorta and/or main branches but also coronary and pulmonary arteries. The course of the disease is unpredictable and management is based on controlling inflammation and preventing end-organ damage. In this case we describe a patient with progression of vasculitis but so far successful prevention of possible ischemic consequences using immunosuppressive and biologic therapy and multiple surgical interventions over the course of the disease. A 14-year-old girl presented with precordial pain and numbness of the left arm. Physical examination revealed the absence of the radial pulse in the left arm. Computed tomography angiography showed subtotal occlusion of the left main coronary artery, subtotal occlusion of the left common carotid artery, subtotal occlusion of the left subclavian artery and stenosis of thoracic aorta below isthmus of aortae. Despite aggressive conservative therapy and cardiocirculatory treatment the course of the disease was complicated with restenoses which were resolved with subsequent revascularization procedures. Here we present an adolescent girl with progressive vasculitis and with multiple surgical interventions. Carefully monitoring of the patient and good collaboration between pediatric cardiologist and rheumatologist with radiologists and cardiac surgeons improved life-quality of the patient which now studies at the University and has good physical and mental status.

**Key words:** childhood Takayasu arteritis, progressive course, surgical interventions, revascularization

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**Abbreviations:** c-TA: childhood Takayasu arteritis; CT: computed tomography; EULAR: European League Against Rheumatism; PRINTO: Pediatric Rheumatology International Trials Organization; PReS: Pediatric Rheumatology European Society

### INTRODUCTION

Childhood Takayasu arteritis (c-TA) is rare but the commonest large vessel vasculitis in children, its incidence has been estimated to be 2,6/1,000,000 per year and it occurs more frequently in girls (1). Etiology is not completely understood but general theories in-

clude genetic factors, infections and activation of both humoral and cell-mediated immunity which lead to inflammation, tissue damage, scarring and stenoses of large vessels (2). Diagnosis is made upon European League Against Rheumatism (EULAR)/Pediatric Rheumatology International Trials Organization (PRINTO)/Pediatric Rheumatology European Society

(PReS) criteria which include pathology in angiography (magnetic resonance angiography is preferable in children to minimize exposure to radiation) plus one of the following: absence of peripheral pulses/ claudication, asymmetrical blood pressure between arms, murmur over great arteries, hypertension or signs of systemic inflammation (elevated markers of inflammation) (3). Therapy options include early initiation of glucocorticoids, symptomatic therapy with beta-adrenergic blockers, calcium channel blockers and ACE inhibitors, use of immunosuppressive agents and surgical interventions (4). The course of the disease in our patient was progressive and complicated by new stenoses and restenoses after initial surgical treatment which required revascularization interventions.

### PATIENT PRESENTATION

A 14-year-old girl presented to our Clinic with angina and numbness of the left arm. Physical exam revealed no palpable pulses in the left arm and arterial hypertension. Laboratory examination demonstrated elevated markers of inflammation (ESR 75 mm/h, CRP 50,9 mg/L). After initial examination and laboratory evaluation the diagnosis of c-TA was suspected. The patient was subjected to computed tomography (CT) angiography which showed subtotal occlusion of the left main coronary artery, subtotal occlusion of the left common carotid artery, subtotal occlusion of the left subclavian artery and stenosis of the thoracic aorta below isthmus of aortae. According to EULAR/PRESS/PRINTO classification (3), our patient fulfilled the following criteria: angiographic pathology plus four out of five additional criteria (absence of peripheral pulses, asymmetrical blood pressure between arms, hypertension and elevated markers of inflammation) so diagnosis of c-TA type IIb (ascending aorta, aortic arch and its branches, thoracic descending aorta) (5), was made. The patient was treated following EULAR recommendations for the management of large-vessel vasculitis (4). We started high-dose glucocorticoid therapy maintained with prednisone and followed by adjunctive therapy with methotrexate and cyclophosphamide. Due to headaches, arterial hypertension, precordial pain and limb ischemia, after three months of initial conservative medical management, complex surgical treatment was performed: subtotal occlusion (90%) of the left main coronary artery was resolved by bypassing occlusion with right mammaria artery into the left anterior descending artery and obtuse marginal branch of the circumflex artery (Figure 1), an ascending aorta to the left carotid artery and left carotid artery to the left axillary artery conduits were placed to resolve stenoses of the left common carotid artery and subtotal occlusion of the left subclavian artery

(Figure 2). Finally, a stent was inserted into the stenotic descending thoracic aorta (Figure 3c). Two months after surgical repair severe flare of the disease occurred so biologic therapy (rituximab) was introduced. Despite aggressive conservative and surgical management over the next two years, the girl developed stenosis of the proximal segment of previously inserted conduit between an ascending aorta to the left common carotid artery (Figure 3a) and additional stenosis of the right common carotid artery. An anastomosis between left and right carotid artery was created (Figures 2, 3b) and stent was placed into the stenotic segment between ascending aorta and the left carotid artery (Figure 3c). In the following course, due to further stenosis of the right common carotid artery, an anastomosis between right subclavian artery and distal segment of the right common carotid artery, just above the stenosis, was made (Figure 2). After complex and multiple surgical interventions the patient is in good condition, she studies at the University and her NYHA score is I-II. At the latest follow-up she was complaining about postprandial abdominal pain so she was admitted to hospital. Clinical presentation of abdominal angina required exclusion of mesenteric ischemia. CT angiography showed completely normal abdominal aorta and branches. Currently we are investigating the other possible causes of the abdominal pain having in mind rare but possible coexistence of c-TA and inflammatory bowel disease. Also due to the signs and symptoms of left hand ischemia, we performed CT angiography which showed a subocclusive lesion of the left axillary artery, about 40 mm long. Therefore, with left transradial approach, we performed a successful endovascular revascularization of the left axillary artery by using a 4×40 mm balloon predilatation (Armada 18, Abbott Vascular, USA) and implanted a heparin stent graft with dimension 5×50 mm (Viabahn, Gore, USA) (Figure 4).

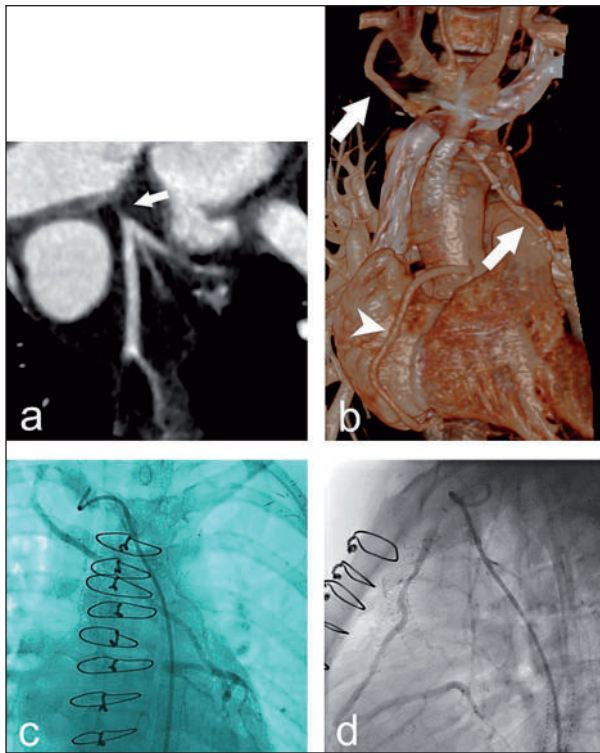


Figure 1. a) Coronary CT angiography, multiplanar reformation. Subocclusive stenosis (lesion) of left main (LM) coronary artery (arrow). b) Coronary artery bypass graft (arrows): right internal mammary artery (RIMA) revascularizing left anterior descending (LAD) and obtuse marginal (OM) arteries. Normal right coronary artery (arrowhead). c) Coronary angiography of the LM coronary artery bypass with RIMA to the circumflex artery. Normal coronary perfusion after intervention. d) Coronary angiography, lateral view.

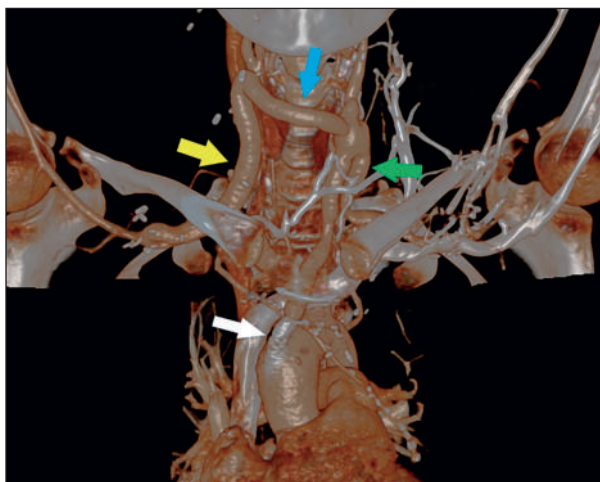


Figure 2. CT angiography – bilateral subocclusion/stenosis of common carotid artery (ACC), and left subclavian artery. Bypass from ascending aorta to the left ACC and stent placement into the stenotic part (white arrow). Bypass from the left ACC to the left axillary artery (green arrow), bypass between right and left ACC (blue arrow), bypass from the right subclavian artery to the right ACC (yellow arrow).

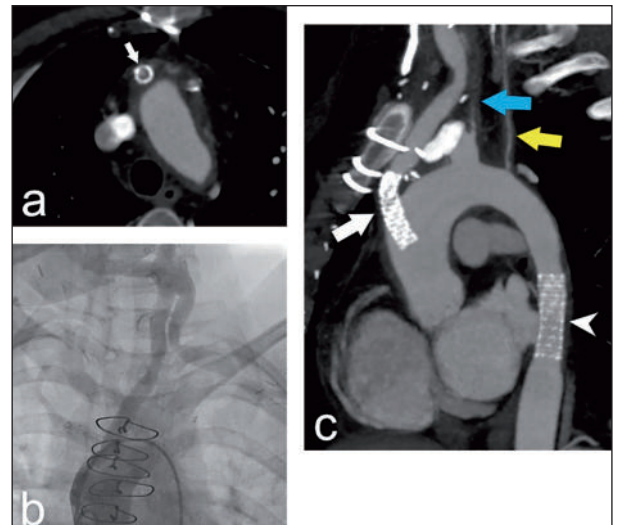


Figure 3. a) CT angiography- restenosis in the stent placed at the stenotic part of the bypass between ascending aorta and left ACC (white arrow). b) Catheter angiography - stenosis of the bypass between ascending aorta and left ACC. Bypass between left ACC and left axillary artery due to stenosis of the left subclavian artery. Bypass between left and right ACC due to severe stenosis of the right proximal part of ACC. c) CT angiography – stent placed into aortocarotid (left) bypass (white arrow), stent placed in stenotic part of descending aorta (arrowhead). Subocclusive stenoses of the left ACC (blue arrow) and left subclavian artery (yellow arrow).

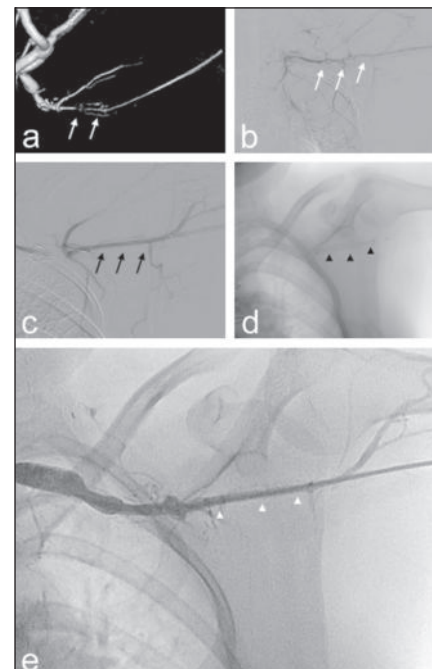


Figure 4. a) b) CT angiography (VRT reformatted image) and DSA angiography, subocclusive lesion of left axillary artery and numerous collateral arteries (white arrows) c) Significantly better width and normal patency of the artery after balloon predilatation (black arrows) d) Stent graft endoprosthesis with heparin bioactive surface implanted in axillary artery (black arrowheads) e) Normal width and patency of the axillary artery after stent graft implantation, with significantly lesser collateral arteries (white arrowheads).



## DISCUSSION

Takayasu arteritis can be very challenging due to unpredictable and progressive course of the disease and possible endorgan damage. There have been no randomized therapeutic trials in pediatric patients and most evidence has been derived from studies performed in adults (2). In 2009, EULAR established recommendations for the management of large vessel vasculitis in adults (4). Russo and Katsicas have listed efficacy studies in Takayasu arteritis including pediatric patients (2). Recently published European consensus-based recommendations for diagnosis and treatment of rare pediatric vasculitides - the SHARE initiative, concluded, considering the lack of evidence in children, that EULAR recommendations may be used in paediatric Takayasu arteritis patients. It also acknowledged reports of the use of TNF-blockade, anti-IL-6 therapy and/or rituximab for severe disease (6). According to EULAR recommendations and SHARE initiative, reconstructive surgery for Takayasu arteritis should be performed in the quiescent phase of disease in the expert centres. Surgery during acute phase of the disease carries significant risk of re-occlusion and procedural complication (4,6). Arterial reconstruction and bypass grafting may be necessary in up to 70% of patients with Takayasu arteritis (4). In children, at least one third will require surgical interventions (2). The indications for surgical intervention include: hypertension from stenotic coarctation of the aorta or renovascular disease, end-organ ischemia or peripheral limb ischemia, cerebral ischemia, aortic or other arterial/cardiac aneurysms, or aortic regurgitation (6,7). Revascularization procedures may be open surgical (bypass interventions) or endovascular (stenting or balloon angioplasty). Both procedures carry substantial risk for the most common complication - restenosis of the vessel undergoing intervention (8). There are few studies in perioperative, short- and long-term outcome of the vascular procedures in children with c-TA but they concluded that children could benefit from this procedures with low mortality, morbidity, and satisfactory long-term results (9,10). Our patient had supra-aortic, subclavian, thoracic and coronary involvement. In adults, surgical approaches vary between different expert centers. For supra-aortic disease, open surgery is recommended with aorto-carotid bypass being the most commonly used technique. Upper limb claudication is one the most frequent indications for revascularization procedures but some centers recommend to avoid interventions if possible and advise upper limb exercise to promote development of collateral circulation. Treatment of thoraco-abdominal lesions include open surgery using prosthetic grafts or endovascular approaches using stent grafts (11). For coronary artery involvement literature suggests coronary artery bypass grafting which

is associated with better long term results (8,11). Our patient reported symptomatic improvement after surgical management. During follow-up period we carefully monitor her clinical and laboratory status and depending on her symptoms and signs we performed follow-up imaging. Good collaboration between pediatric cardiologists/rheumatologists and radiologists, ophthalmologists, nephrologists, neurologists and vascular/cardiac surgeons guaranteed good assessment of the disease. The course of c-TA is progressive with repeated flares and need for continuous immunosuppressive therapy (2). Recently published the largest study describing the clinical course and prognostic factors associated with rehospitalization of 101 Chinese pediatric patients with c-TA, found that type IIb in their cohort, represents 3.1-fold risk predictor of c-TA relapse and indicates a trend for vascular complications. They also showed revascularization to be an independent protective factor of fewer events and flares in c-TA. Finally they concluded that the stroke, elevated CRP, lower BMI level, and younger age at admission are independent risk factors of poor outcomes (12). Despite flares and multiple surgical interventions, our patient is in good condition (NYHA I-II), her blood pressure is well controlled (<90.c.), her latest markers of inflammation are normal and she succeeds to manage all school responsibilities.

## CONCLUSION

Due to rarity of the disease and lack of evidence in treating children with Takayasu arteritis it can be very challenging to manage this condition in pediatric population. Early diagnosis, regular clinical, laboratory and imaging follow-up, adequate therapy (conservative and surgical) and finally, cooperation between specialists can provide good quality of life to the patients.

## R E F E R E N C E S

1. Kerr GS, Hallahan CW, Giordano J *et al.* Takayasu arteritis. *Ann Intern Med* 1994; 120(11): 919-29. doi: 10.7326/0003-4819-120-11-199406010-00004.
2. Russo RAG, Katsicas MM. Takayasu Arteritis. *Front Pediatr* 2018; 24(6): 265. doi: 10.3389/fped.2018.00265.
3. Ozen S, Pistorio A, Iusan SM *et al.* EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis* 2010; 69(5): 798-806. doi: 10.1136/ard.2009.116657.
4. Hellmich B, Agueda A, Morti S *et al.* Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis* 2000; 79(1): 19-30. doi: 10.1136/annrheumdis-2019-215672.

5. Moriwaki R, Noda M, Yajima M, Sharma BK, Numano F. Clinical manifestations of Takayasu arteritis in India and Japan – new classification of angiographic findings. *Angiology* 1997; 48: 369-79.
6. de Graeff N, Groot N, Brogan P *et al.* European consensus-based recommendations for the diagnosis and treatment of rare paediatric vasculitides - the SHARE initiative. *Rheumatology (Oxford)*. 2019; 58(4): 656-71. doi: 10.1093/rheumatology/key322
7. Perera AH, Mason JC, Wolfe JH. Takayasu Arteritis: Criteria for Surgical Intervention Should Not Be Ignored. *Int J Vasc Med* 2013; 2013: 618910. doi: 10.1155/2013/618910.
8. Misra DP, Wakhlu A, Agarwal V, Danda D. Recent advances in the management of Takayasu arteritis. *Int J Rheum Dis* 2019; 22 Suppl 1: 60-8. doi: 10.1111/1756-185X.13285.
9. Kalangos A, Christenson JT, Cikirikcioglu M *et al.* Long-term outcome after surgical intervention and interventional procedures for the management of Takayasu's arteritis in children. *J Thorac Cardiovasc Surg* 2006; 132(3): 656-64.
10. Reddy E, Robbs JV. Surgical management of Takayasu's arteritis in children and adolescents. *Cardiovasc J Afr* 2007; 18(6): 393-6.
11. Mason JC1. Surgical intervention and its role in Takayasu arteritis. *Best Pract Res Clin Rheumatol* 2018; 32(1): 112-24. doi: 10.1016/j.berh.2018.07.008.
12. Fan L, Zhang H, Cai J *et al.* Clinical course and prognostic factors of childhood Takayasu's arteritis: over 15-year comprehensive analysis of 101 patients. *Arthritis Res Ther* 2019; 21: 31. doi: 10.1186/s13075-018-1790-x. Correction in: *Arthritis Res Ther*. 2019; 21: 55.

## SAŽETAK

### DJEVOJKA S TAKAYASU ARTERITISOM PROGRESIVNOG TIJEKA S MULTIPLIM KIRURŠKIM INTERVENCIJAMA

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Takayasu arteritis je vaskulitis velikih krvnih žila koji zahvaća aortu i njezine ogranke ali i pulmonalne i koronarne krvne žile. Tijek bolesti je nepredvidiv i terapija obuhvaća smirivanje upalnog procesa i prevenciju oštećenja organa. Prikazujemo bolesnicu s progresivnim tijekom bolesti koji je zasada uspješno obuzdavan uz pomoć imunosupresivne i biološke terapije kao i multiplim kirurškim postupcima. 14-godišnja djevojčica se očitovala prekordijalnim bolovima i utrućem lijeve ruke s gubitkom pulsa radijalne arterije. CT angiografijom je nađena totalna okluzija debla lijeve koronarne arterije, subtotalna okluzija lijeve zajedničke karotidne arterije i lijeve potključne arterije te stenoza torakalne descendente aorte ispod razine istmusa. Unatoč agresivnoj konzervativnoj terapiji i kardiokirurškom tretmanu daljnji tijek bolesti je kompliciran restenozama koje su razriješene postupcima revaskularizacije. Pažljivim praćenjem bolesnice kao i dobrom suradnjom pedijatrijskih kardiologa i reumatologa s kardiokirurzima te radiolozima omogućena je dobra kvaliteta života u djevojke koja se uspješno školuje te je u dobrom fizičkom i mentalnom stanju.

**Ključne riječi:** pedijatrijski Takayasu arteritis, progresivan tijek, kirurške intervencije, revaskularizacija