

Report on Takayasu Arteritis in Three Iranian Children

Mohammad-Hassan Moradinejad*¹, MD; Vahid Ziaee^{1,2}, MD; Abdorazagh Kiani¹, MD;
Parviz Karimi¹, MD

1. Department of Pediatrics, Tehran University of Medical Sciences, Tehran, IR Iran
2. Growth and Development Research Center, Tehran University of Medical Sciences, Tehran, IR Iran

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Abstract

Background: Takayasu arteritis (TA) or giant cell vasculitis is the third common vasculitis after Henoch-Schoenline purpura and Kawasaki disease in children. This vasculitis usually affects large vessels and is more common in females during the childhood. Aim of this report is to present three Iranian children (two boys, one girl) with TA.

Case Presentation: Mean age of our cases on admission was 10 years. Patients most commonly presented with episodes of systemic symptoms including, fever, headache, increased arterial blood pressure in one limb and convulsion. Other related symptoms were myalgia, limb pain, chest pain, and abdominal pain. Supra sternal, and abdominal bruit was noted in all patients. Angiography was performed in all cases. This revealed stenosis of the left subclavian artery and common carotid artery in one patient, generalized aortitis in one case and stenotic right renal artery in one patient. One boy was diagnosed as having systemic onset of juvenile idiopathic arthritis. One case was referred with hand pain and headache, and one case for control of hypertension. Follow-up ranged from 2 to 7 years since diagnosis. All patients were treated with prednisone, azathioprine, aspirin, and antihypertensive drugs. Each patient received either methotrexate, or hydroxychloroquine or mycophenolate mofetil.

Conclusion: Although TA is uncommon before 10th year of life, it should be considered in patients presenting with hypertension and systemic symptoms such as fever, limb pain and pulseless limb.

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Introduction

Takayasu's arteritis (TA) or pulseless disease is a non-specific arteritis affecting predo-

minantly the aorta and its major branches. It is the third chronic idiopathic vasculitis in children [1,2]. First case of TA disease was described by Dr Mikito Takayasu in 1908 at

* **Corresponding Author;**

Address: Division of Pediatric Rheumatology, Children's Medical Center, Pediatrics Center of Excellence, Dr Gharib St, Keshavarz Blvd, Tehran, IR Iran

E-mail: moradine@tums.ac.ir

the Annual Meeting of the Japan Ophthalmology Society [1]. Cause of TA is unknown[2]. TA occurs most commonly in females in the second and third decades of life, but has also been reported in children aged under 16 years. Report on TA in children is rare. Clinical manifestations of TA have two phases: systemic phase and occlusive phase [3]. In systemic phase, patients have non-specific symptoms such as fever, weight loss, fatigue, and non-specific aches and sometimes arthritis. In the occlusive phase symptoms begin due to narrowing of affected arteries.

During the occlusive phase, affected arteries may be narrowed with absent normal arterial pulsations (pulseless)[2]. Other findings include pain in the elbow, wrist, or lower extremities (claudication) [4]. This disease is not common in children. Its treatment in pediatrics has been limited to high dose prednisolone, and immunosuppressive drugs (methotrexate, cyclophosphamide and mycophenolate mofetil) [5]. The aim of the present report was to report TA in three cases in a referral pediatric rheumatology clinic in Iran, from 2002 to 2007, with emphasis on clinical manifestation and medical management. In this report we used EULAR (European League Against Rheumatism)/PReS (Paediatric Rheumatology European Society) classification criteria for TA diagnosis[5]. EULAR/PReS classification criteria for TA diagnosis are: (1) claudication or decreased peripheral artery pulses, (2) blood pressure difference >10 mm Hg, (3) bruits of the aorta or its major branches, and (4) hypertension.

Cases Presentation

Case 1: An 8.5 year-old-boy was referred with unremarkable family or past medical history.

He was admitted at the age of 7 years for hypertensive encephalopathy (BP 170/100 mmHg) and convulsion. Symptoms started two days prior to admission with headache and vomiting. His parents reported a history

of fatigue, malaise, myalgia, arthralgia, and weight loss (4 kg) in the last 2 years. On admission he was alert, afebrile without distress. Blood pressure was 170/100 mmHg. Left hand was pulseless, puls in other limbs was normal. An audible bruit was heard over left subclavian arteries and aorta. Other clinical findings in physical examination were normal.

Laboratory investigations on admission revealed anemia (Hb 9.5 g/dl), thrombocytosis (platelet count 565000), white blood cell 20.000, ESR 95 mm/h, CRP 40 mg/L, autoantibody tests (F-ANA, C-ANCA, P-ANCA) were negative, and serum creatinine, electrolytes, urinalysis, as well as ECG and chest X-ray were normal. An echocardiogram showed mild thickening of the left ventricle.

Magnetic resonance angiography (MRA) demonstrated narrowing in the left subclavian artery, the descending thoracic aorta, and right renal artery (Fig 1). Patient was given prednisone 2 mg/kg per day, azathioprine 2mg/kg, antihypertensives (amlodipine 5 mg/day, enalapril 10 mg/day), as well as low-dose aspirin. After 2 weeks, ESR fell to 26 mm/h and BP to 156/86 mm Hg. Vascular surgeon refused the vascular surgery.



Fig 1: Magnetic resonance angiography image from patient 1 with active Takayasu's arteritis at diagnosis. There is complete occlusion of the left subclavian artery at its origin with numerous collaterals evident and an ostial stenosis of the left common carotid artery.

When the prednisolone was tapered to 5mg per day relapse occurred. So, daily dosage was increased up to 40 mg (1 mg/kg/d), and another immunosuppressive [mycophenolate mofetil (MMF) 1000 mg daily] was added for two months. After 2 months clinical symptoms and signs and laboratory tests returned to normal. He was discharged with prednisone 10 mg/day, azathioprine 25 mg/day, MMF 250 mg daily, enalapril 10 mg/day and low-dose aspirin.

At the age of 14 years, he was taking prednisone 7.5 mg per day, MMF (250 mg daily), enalapril 5 mg/day, and low-dose aspirin. BP was 135/65 mmHg. The last laboratory tests showed ESR 28 mm/h, Hb 115 g/dL, platelet count 557 G/L, and normal renal function. Last MRI angiogram showed normal left common carotid artery, left subclavian artery, descending thoracic aorta and right renal artery. Neurological examination was normal, but periodic headache was still present.

Case 2: An 11-year-old girl was referred with fever, fatigue and malaise with a 3-week history of numbness and claudication in the left arm, pain in extremities, dyspnea, palpitations, headache and weight loss. Systolic arterial blood pressure was 100 mmHg in the left arm and 140 mmHg in the right arm. On initial physical examination, signs of vascular insufficiency including pulse discrepancy of greater than 40 mmHg between the right and left arm were detected. Other significant finding was vascular bruit, most commonly in the carotid but also in the subclavian arteries.

Laboratory tests showed a considerable rise in ESR (100 mm/1h) with white blood cell count 7800/ μ L; hemoglobin, 10.0 g/dL; platelets 500000/ μ L. Blood urea nitrogen, creatinine, electrolytes, thrombin and partial thromboplastin time were all within normal limits and an ECG showed sinus tachycardia. A recent aortogram demonstrated severe stenosis of the innominate and left subclavian

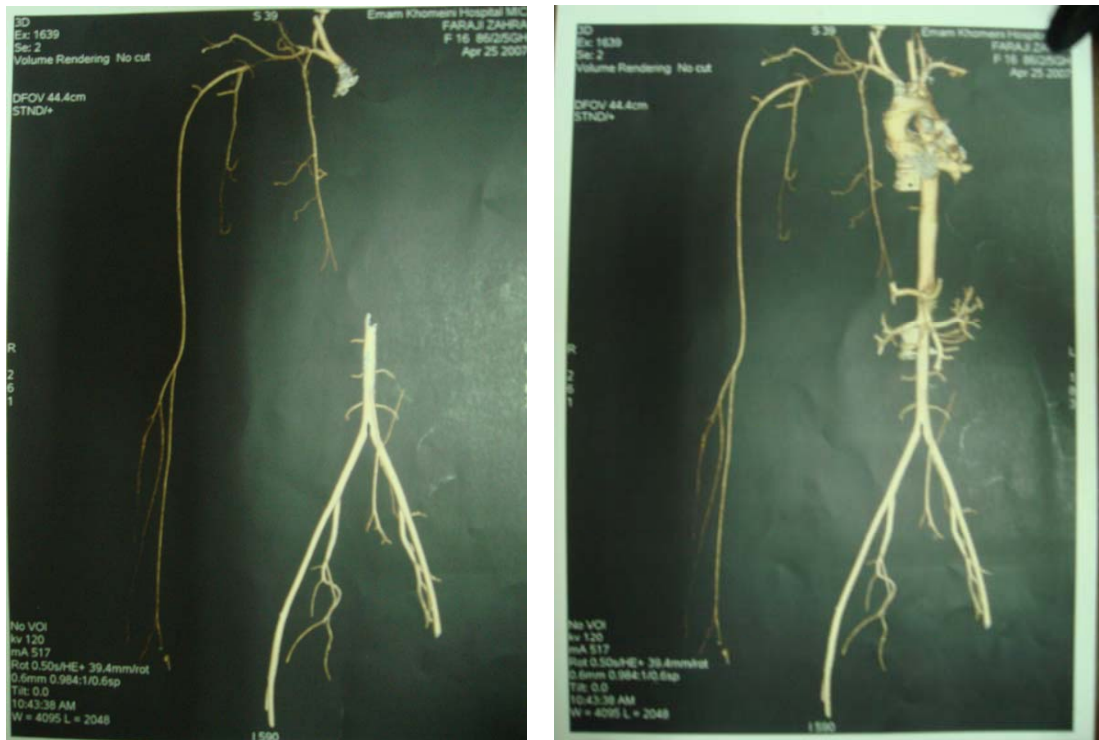


Fig 2: Angiography of the great vessels. Right fig showing a 4 cm occlusion of the of left subclavian artery and left fig demonstrating retrograde filling of the subclavian via the left vertebral artery.

artery (Fig 2). Medical therapy consisted of prednisone 2mg/kg, methotrexate 10mg/wk, and azathioprine 50mg/day, aspirin 80 mg/day and enalapril 10mg/ bd. She was discharged after 3 weeks with prednisone 10 mg/day, azathioprine 25mg/day, methotrexate 5mg/wk, enalapril 10mg/day and aspirin 80 mg/day. In a visit 1 year later, BP was 135/65 mmHg. Now her medication is prednisone 7.5 mg per day, azathioprine 25 mg/day, enalapril 10 mg/day, and aspirin 80 mg/day.

Case 3: An 11-year-old male referred for episodic fever, malaise, headache, weight loss and arthralgia. He suffered from nausea and vomiting. In his medical history, he had episodic headache and pain in lower and upper limbs for 2 years. He has been treated as systemic onset of juvenile idiopathic arthritis (JIA) in previous centers. In recent episode we found increased blood pressure (230/80 mmHg). Family history was negative. In addition to hypertension, we found aortic pulse and murmur in abdominal examination. Left radial and axillary arteries were pulseless and the pulses in lower limbs were undetectable.

Significant laboratory tests included: white blood cell count 28,400/ μ L, hemoglobin 10.6 g/dL, platelet 442,000/ μ L. ESR: 95 mm/1h, CRP 6.7 mg/dL and fibrinogen 576 mg/dL. PT, PTT, BUN, Cr and complete metabolic panel were normal.

Ecocardiography was normal with no evidence of coarctation. Color Doppler ultrasound examination revealed severe narrowing of the abdominal aorta with collateral aortriols supplying both kidneys. Ascending and descending pressures were 140/95 and 75/65, respectively. Angiography of descending aorta showed significant inflammation and narrowing of the distal thoracic aorta and abdominal aorta beyond the origin of the renal arteries.

Treatment started with prednisone 2 mg/kg/day, aspirin 100 mg/kg/day, and hypertension was controlled by adalat and captopril. After 4 weeks, ESR decreased to 30 and blood pressure was 120/75. In addition, he was on cyclophosphamid pulse therapy

monthly for 4 pulses. After 12 months, there is no evidence of disease activity and renal function was normal. A weight gain more than 10 kg during 12 months had been registered

Discussion

TA is a rare vasculitis in children especially in children younger than 10 years. In a Turkish multicenter series report (2007), TA was represented in 1.5% of pediatric vasculitises^[6]. The most common clinical manifestations of Takayasu's arteritis are non-specific symptoms such as; fever, night pain, malaise and weight loss ^[7]. Most important clinical features of TA are absent arterial pulses in the upper limbs, high blood pressure, headache, dizziness and weakness ^[8].

Loss of wrist pulses and claudication due to irregularity, narrowing, fibrosis, thickening, and stenosis affected vessels are other signs ^[4].

Other non-specific manifestations are arthralgia and myalgia; some patients develop true arthritis. Less commonly, lupus-like rashes and erythema nodosum may be present.

Female to male ratio has been reported 4.4-5:1^[9,10]. The youngest patient was 3 years old^[9].

Arterial hypertension is the most common presenting symptom in 83-93% of the patients ^[9-12]. This is followed by cardiac failure, bruits, and absent pulses ^[11]. Although there is a predominant involvement in females, in our report 2 patients were males. Two male patients had significant hypertension symptoms. Peripheral pulses are often absent due to vascular obstruction. In our study 2 patients had no pulse in the involved limb and one of them had a pulse discrepancy of greater than 40 mmHg between the 2 limbs. In Turkish multicenter series, half of the patients had involvement of both thoracic and abdominal aorta ^[6]. In our study one patient had both thoracic and abdominal involvement and two others had thoracic or abdominal aortic involvement.

Our patients had fulfilled the ACR criteria for adult TA^[3], and PReS classification criteria for TA diagnosis in children^[5]. The diagnosis of TA is based on characteristic clinical findings, involvement of aorta and its major branches seen on sonography and angiography^[7,8,13].

We followed our patients with color Doppler sonography as non-invasive modality. Color Doppler sonography gives an accurate global evaluation of the aorta and branches of arterial tree, by disclosing most of the inflammatory localizations in accessible arteries, thus being particularly useful in the long term evaluation of disease activity^[14,15]. In the early phase of the disease, when the basic pathologic features are mural changes of the great vessels and luminal abnormalities are still not evident, the subclavian artery involvement is considered the commonest finding of the disease (in about 90% of patients)^[14]. Well known are the limits of the Doppler sonography in exploring the deep intrathoracic structures, like the proximal part of the subclavian artery. In this phase, angiography may not show any intraluminal changes of aorta and its branches; an indirect sign of aortic wall thickening is the increase in the distance between opacified lumen of the descending thoracic aorta and the air in the lung. The best modality for TA confirmation is angiography or MRI angiography^[6,7]. The most common lesion is a smooth, concentric, arterial or aortic narrowing^[16]. Irregular narrowing, complete occlusion and fusiform or saccular aneurysms are less commonly seen^[8,13]. The gold standard for diagnosis of vasculitis still is angiography technique for conditioning luminal abnormalities. But it is an invasive technique, calling for an arterial access for central positioning of the injecting catheter; generally axillary or femoral route access may be needed in cases of total occlusion of the abdominal aorta.

With regard to imaging studies, traditionally the angiographic patterns have been divided into type I, affecting the aortic arch; type II, the thoracic and abdominal aorta; type III, the aorta both above and below the diaphragm; and type IV, the aorta and the

pulmonary arteries^[6,7]. In our cases type I was the predominant pattern, whereas in two series type II was the predominant one. Our patients were followed from 1 to 5 years since diagnosis (mean 3 years) and the last treatment consisted of low-dose prednisone, anti-hypertensives, low-dose aspirin and methotrexate. One of them still needed MMF. Methotrexate has been used both in adults and children with good results^[17,18].

MMF has also recently been introduced in the treatment of adult patients^[19]. Our patients had a good clinical response to combination therapy. There may be episodes of remission and relapse, and good response is to expect when MMF is administered.

TA is a disease with severe prognosis, mortality rate being reported in children from 35 to 40% by five years^[20].

Conclusion

TA should be considered in young patients with unexplained arterial hypertension and also in cases of unexplained fever, unexplained inflammatory syndromes without localized signs.

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