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A Case series of Childhood-onset Takayasu Arteritis

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Childhood-onset Takayasu disease(c-Tak) is a rare chronic granulomatous disorder involving large vessels. It is the 3rd most common vasculitis in childhood. It is diagnosed based on criteria laid by European League Against Rheumatism/ Pediatric Rheumatology International Trials Organization/Pediatric Rheumatology European Society criteria. Treatment is mainly based on corticosteroids and immunosuppressive therapy. We are reporting case series of c-Tak due to their varied presentations.

Keywords: Childhood-onset Takayasu, Pediatric rheumatology, Vasculitis

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Introduction

Childhood-onset Takayasu arteritis(c-Tak) is a rare chronic granulomatous disease of the large vessel seen in children. It involves the aorta, its branches, and the pulmonary arteries [1]. The large vessels undergo stenosis, occlusion, or dilatation following inflammation. The exact etiology and pathogenesis remain unknown. Its spectrum of presentation varies and is mainly due to vascular occlusion leading to end-organ ischemia. According to revised criteria in 2010[2], in children, angiographic abnormality, with aneurysm or dilatation, narrowing, occlusion, or thickening of the aorta or its main branches, is a mandatory criterion for the diagnosis. In addition to this mandatory criteria, at least one of the following should be fulfilled: pulse deficit or claudication, blood pressure discrepancy > 10 mm Hg in any limb, hypertension with systolic or diastolic > 95th centile for height, and erythrocyte sedimentation rate (ESR) > 20 mm/h or elevated C-reactive protein (CRP). Here we are reporting case series of Takayasu arteritis in children with varied presentations.

Case 1

A 15-year-old, developmentally normal, well immunized female child was admitted in April 2019 with complaints of palpitation and fatigue on mild activity for 7-8months. She developed palpitation and weakness of all four limbs on exertion. Each episode lasted for 3-5mins which improved on taking rest. The symptoms were non-progressive and equal in all four limbs. There was no history of chest pain, claudication, headache, vomiting, fever, excessive sweating. She is a known case of hypertension and on antihypertensives carvedilol, chlorothiazide, and prazosin for eight months. She had irregular menses with a 1-2 months gap with a normal flow of 2-3 days without pain. Her appetite was normal. On General examination, the child was conscious, alert with a normal gait. Her pulse rate was 112/min, well felt in the upper limb, not palpable in the lower limb. Her BP in right upper limb-160/120mm Hg, left upper limb-160/120mmHg, right lower limb110/88mmHg, Left Lower limb-100/66mm Hg. Her respiratory rate was 18/min, and the temperature was 98◦F. There was mild pallor, no icterus, no cyanosis, clubbing or lymphadenopathy, no edema, JVP was not raised. Her height was152.4 cm, and her weight was 33kg which comes under moderate malnutrition.

On systemic examination, cardiovascular system examination revealed heaving type apex, loud S1, systolic murmur at the aortic area, palpable thrill at the apex. The abdomen was soft; no organomegaly with a bruit over the epigastrium was found. Respiratory and CNS examinations were normal. The ophthalmological evaluation suggested normal vision with normal fundus. ECG showed sinus tachycardia with normal axis, LVH, bifid P wave, No ST-T abnormalities.2D-Echo revealed mild concentric LVH, mild global hypokinesia, Grade 1 diastolic dysfunction 54.2% (secondary to hypertension), Trivial AR. Renal artery Doppler showed Short segment circumferential wall thickening involving abdominal aorta, beyond the origin of SMA, causing50-60% luminal narrowing, extending to involve the origin of bilateral renal arteries resulting in bilateral renal artery stenosis. CT aortogram showed diffuse circumferential, long segment wall thickening involving the distal descending aorta & proximal abdominal aorta, extending from the level of D8 to L3 vertebra, suggesting aorto-arteritis causing bilateral renal artery stenosis. Lung appears normal, no mediastinal lymphadenopathy, abdominal organs appear normal, both kidneys showed normal enhancement pattern with normal excretion of contrast. She was undergone blood investigations to rule out vasculitis.

Her CBC was normal,ESR-46,CRP-10.4mg/L,ANA-ve,p ANCA & c ANCA –ve.HBs Ag,HCV,HIV –ve,Serum urea 40,creatinine 0.6,uric acid 5.6mg/dl,PT.INR13,1.01 –N.Urine metanephrine-160.9microgm/24 hrs urine.(N:25-312) within normal limit.Thyroid function test :TSH 1.57micro IU/ml(0.5-4.3),FT3-3.11pg/ml(2-4.4),FT4-1.64ng/ml(0.93-1.70)within normal limit.The child was diagnosed to be Takayasu arteritis type III,clinical class IIB. During hospital stay child's BP was 140/88mm Hg with antihypertensive amlodipine 10mg once daily,tab Cilnidipine10mg once daily,Tab.labetolol 200mg twice daily and T prednisolone 2mg /kg/day.Child was continued on methotrexate on follow up and aortic angioplasty and renal artery angioplasty and stenting was done.

Case 2

11-year-old male child k/c/o Takayasu arteritis Type 4 (diagnosed in Dec 2011at age of 4yrs) got admitted on Feb 13, 2020, with the headache for 20 days and complaints of chest pain on the left side, pain over the left thigh for two days.

On examination, the child was afebrile, pulse was 60 /min, and upper limb and lower limb BP differences were not noted. Peripheral pulses were well felt, and the rest of the examination was normal. The patient was initially on MMF 500. He was worked up for disease activity by CRP, ESR, which came to be normal. ECG and Echo were normal. There is no history of breathlessness. CT angiography of coronary and thoracic was done, which was reported to be normal.

The child was started on methotrexate @10mg/m2/week, and MMF was tapered. Oral Prednisolone was given for five days and stopped. As a family stressor was present and clinically, we could not elicit any cause of new-onset pain, hence Psychiatry opinion was done and was diagnosed to be Acute stress disorder VS adjustment disorder and started on Escitalopram and Clonazepam. His investigation showed normal CBC, RFT, LFT and normal ESR, CRP with only insufficiency of Vit D.

Case 3

7 yr female child born out of non-consanguineous marriage, developmentally normal, got admitted on Oct 1, 2019, with 1 episode of seizure three days back, associated with loss of consciousness and weakness of right side of body and deviation of angle of mouth. The child had a history of right-sided weakness one year back and recovered gradually. She had taken some ayurvedic medication.

On examination, the child was conscious, oriented, pulse 80/min, not palpable in upper limb but palpable in the lower limb.BPwas 88/72mm Hg in the upper limb and 138/90 mm Hg in the lower limb. Her respiratory rate was 20/m, and she was afebrile.

There was mild pallor, no icterus, no cyanosis, no clubbing, no lymphadenopathy. Child weight was 17kg, height was 114cm s/o underweight. Right-sided hemiparesis was present with power 3/5, exaggerated reflex, and extensor plantar on the right side. Left sidetone, power, reflex were normal with plantar flexor with Rt UMN type facial palsy. A provisional diagnosis of Takayasu arteritis with stroke was made. She was started on in. Levetiracetam, aspirin, and given NG feeding, fundus showed no hypertensive changes in the retina. Amlodipine was started, and BP was controlled to 90th centile.

Her CBC, LFT, RFT were normal, CRP-20, ESR-40 raised, ANA came negative and gastric aspirate for AFB staining, and CBNAAT for tuberculosis were negative. She was started on immunosuppressant Prednisolone followed by methotrexate. Echocardiography was done, showed a normal study. CT angiography showed B/L common carotid block with proximal segment involvement, left side marked obstruction, and few collaterals present, B/L subclavian also involved. CTVS call and interventional radiology opinion were taken. During the hospital stay child gradually recovered and started walking but had a repeat episode of hemiparesis over the same side on day 14 of admission; physiotherapy was given, and power improving. The child was planned for DSA and interventional radiology procedure.

Case 4

13-year female child diagnosed with Takayasu arteritis at the age of 10 yrs (June 2016) presented with a hypertensive emergency with a seizure. After that, she was on Prednisolone, aspirin, amlodipine, labetalol, phenytoin. She had residual left-sided hemiparesis after that. She had a breakthrough seizure twice, for which she was given levetiracetam as an add-on antiepileptic. She was admitted in October 2019 with fever and loss of appetite for 20 days. On examination child was afebrile, the radial pulse of right upper limb palpable, left upper limb feeble,dorsalis pedis of both lower limbs palpable. Her blood pressure was 130/90 mmHg in Rt upper limb 110/78mmHg in the lower limb. On CNS examination, tone of both left side upper limb and lower limb increased, power being 4/5 in both left upper and lower limb, reflexes normal with contracture on left ankle and tone, power, reflex being normal in right upper limb and lower limb. Another systemic examination was normal. On investigation, Montoux was strongly positive, Sputum for AFB and CBNAAT –ve, and the chest x-ray suggested tuberculosis. CT scan brain showed chronic infarct with gliosis and encephalomalacia in the right temporoparietal region and right lentiform nucleus.CT aortogram revealed narrowing of the distal arch of the aorta, right subclavian artery, left subclavian artery. The luminal narrowing was seen in the abdominal aorta below the origin of SMA up to the origin of IMA. Markedly narrowing of the right renal artery and mild narrowing of the left renal artery was seen. Patchy area of chronic consolidation with fibrotic change seen in the posterior segment of right upper lobe in CT chest.

Her CBC showed leucocytosis with neutrophilic preponderance. Her ESR was 80, CRP was 60. Blood C/S was sterile. Hence she was started on antitubercular therapy with a plan of the initiation phase of 2 months of HRZE followed by six months of continuation phase with HRE.

The child was continued on antiepileptics oxcarbazepine, levetiracetam and also started on steroid and methotrexate review of increased disease activity.

Table-1: Clinical, laboratory, CT angiography Characteristic of Children with TA

	Case 1	Case2	Case3	Case4
Age of diagnosis	15yr	4yr	7yr	10yr
Gender (M,male:F,female)	Female	Male	Female	Female
Present complaint	Palpitation and fatigue	Headache x20 days Left chest and thigh pain x3days	Seizure	Fever and loss of appetite for 20 days
Pulse deficit	Lower limb pulse absent	No pulse deficit	Pulse deficit in both upper limb	Left radial pulse weak
BP discrepancy	present	Absent	Present	no
HTN	160/120	Normal BP	138/90 in lower limb	130/90
Brut	Epigastric brut	No	No	no
ESR	46	5	40	80
CRP	10.4	1	20	60
CT Angiography	Aortaarteritis(D8-L3) with renal artery stenosis	Aortoarteritis with renal artery stenosis	B/L common carotid block with proximal segment involvement, left side marked obstruction and few collaterals present, B/L subclavian also involved	CT aortogram revealed narrowing of the distal arch of the aorta, right subclavian artery, left subclavian artery. The luminal narrowing was seen in the abdominal aorta below the origin of SMA up to the origin of IMA. Markedly narrowing of the right renal artery and mild narrowing of the left renal artery were seen
Stroke	Absent	Absent	Present	present
Treatment	Methotrexate	MMF tapered, methotrexate started	Prednisolone and methotrexate	Prednisolone and methotrexate
Surgical intervention	Aortic and renal artery angioplasty and stenting	Stenting of the abdominal aorta and renal artery done		

Discussion

Childhood Takayasu disease is 3rd most common vasculitis among children after Henoch schooling Purpura and Kawasaki disease. To diagnose c-TAK, currently, EULAR/PRINTO/PRES childhood TAK (c-TAK) classification criteria (Table 2) are being used, which has sensitivity and specificity around 100% and 99.9%, respectively.[2].

There is no data regarding the exact incidence of c-TA, but European and North American studies have estimated the incidence between 1 to 2.6/1000000 population/year. [3,4]. Usually, the disease commonly presents in the 2nd and 4th decades of life. Childhood-onset TA(c-TA) has been seen in late infancy to adolescent age groups with the peak age of presentation around 12 yr and most minor age at presentation in a 6-month-old baby. [5-7].

It has a 2:1 female: male preponderance according to the Indian and South African series. [8,9]

In our case series, also females (3/4)outnumber male children.

Table 2: EULAR/PRINTO/PRES childhood TAK (c-TAK) classification criteria

Criteria	Glossary
Angiographic abnormality (mandatory criteria)	Angiography (conventional, CT, or MRI) of the aorta or its main branches and pulmonary arteries showing aneurysm/dilatation, narrowing, occlusion, or thickening of the arterial wall not due to fibromuscular dysplasia or similar causes; changes usually focal or segmental plus at least one of the five criteria
1. Pulse deficit or claudication	Lost/decreased/unequal peripheral artery pulse(s) Claudication: focal muscle pain induced by physical activity
2. Blood pressure (BP) discrepancy	Audible murmurs or palpable thrills over large arteries
3. Bruits	Audible murmurs or palpable thrills over large arteries
4. Hypertension	Systolic/diastolic BP greater than 95th centile for height
5. Acute phase reactant	Erythrocyte sedimentation rate >20 mm per first hour or CRP any value above normal (according to the local laboratory)

CT: Computer Tomography; CRP: C-reactive protein; EULAR: European League Against Rheumatism; MRI: Magnetic Resonance Imaging; PRES: Pediatric Rheumatology European Society; PRINTO: Pediatric Rheumatology International Trials Organization

We observed HTN in 3/4 cases, stroke in 2/4 of patients. As described by various literature, hypertension has been the most common symptom in adults and children, and stroke has been described in 17% cases in c-TA and 20-24 % in patients with TA. [10]. Due to peripheral vascular obstruction, often peripheral pulses are not well felt, so it is called 'pulseless disease'.We noticed pulse deficits in ¾ cases. One of the cases was diagnosed to have tuberculosis and started on ATT. There is an association between tuberculosis and Takayasu arteritis in developing countries where tuberculosis (TB) prevalence is more common. There is a description of active tuberculosis up to 20% in adult TA patients. [11]. A strongly positive Mantoux test has been observed in 20% of all TA patients in one study from India. [12]. Whether this association represents a causal relationship or a mere coincidence is still unclear.

Imaging findings: Vascular imaging is essential for the establishment of diagnosis and management of c-TA cases. Table 3 shows the angiographic classification of Takayasu Arteritis. Imaging modalities can be Conventional angiography, Magnetic Resonance Angiography(MRA), Computed Tomography Angiography(CTA), Doppler Ultrasound, and fluorodeoxyglucose positron emission tomography (PET).

In children with TA, the thoracic aorta and abdominal aorta are the most common vessels involved, followed by renal, subclavian and carotid artery. In our series, Abdominal aorta involvement with renal artery stenosis was seen ¾ cases.

Table-3: Angiographic classification of Takayasu arteritis

Type	Vessel involvement
I	Branches from the aortic arch
IIa	Ascending aorta, aortic arch and its branches
IIb	Ascending aorta, aortic arch and its branches, thoracic, descending aorta
III	Thoracic, descending aorta, abdominal aorta, and renal arteries
IV	Abdominal aorta and renal arteries
V	Combined features of type IIb and IV

Treatment: Treatment of TA consists of corticosteroids alone or in combination with immunosuppressive agents like methotrexate, MMF during the progression of the disease. Usually, surgical interventions are required in severe renal artery stenosis resulting in hypertension. [5]. Those who are resistant to immunosuppressive therapy may be offered biological agents. Our two patients received Prednisolone with methotrexate, and two patients received only methotrexate. c-TA is a severe disease with a mortality rate of 35-50% by 5years, as mentioned by previous studies.[13].

Conclusion

Suspicion ofc-TA should be done in children with unexplained hypertension, nonspecific complaints like fatigue in a background of elevated inflammatory markers.

Early evaluation by angiography is important as it guides surgical intervention also. The active disease process has to be managed with corticosteroids and immunosuppressive agents.

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