Chapter

Takayasu Arteritis: Review in Pediatrics

Melisa Rivera, Jose Heriberto López-Beltrán and Blanca Frisia Morales-López

Abstract

Takayasu arteritis (TA) is classified as a large-vessel vasculitis, and it primarily affects the aorta and principal branches. The clinical presentation in pediatric patients is odd and there are few literature about it because of its low incidence and nonspecific clinical presentation. The standardized diagnosis of TA is by imaging support, such as computed tomography (CT) and magnetic resonance imaging (MRI). When using CT, angio-CT is recommended because it will allow us to observe the caliber of the arteries, wall changes, and level of stenosis. The study should include the aortic arch, abdominal aorta, visceral branches, and iliac arteries taking into account that the mainly affected arteries are the left subclavian, abdominal aorta, right renal artery, and descending chest aorta. In the same way in the study, four imaging patterns of TA can be identified: variable decrease in the luminal diameter of the aorta and arteries, total occlusion, fusiform and saccular aneurysm, and irregular contour of the aortic wall. Identifying TA findings is important for early diagnosis, medical management, and proper monitoring specifically in pediatric patients where literature is little available.

Keywords: Takayasu arteritis, large-vessel vasculitis, pediatrics, rheumatology, biological agents

1. Introduction

Takayasu arteritis is a rare vasculitis with no clear etiology presented most of the time in young women. It is even more rare to be presented in children. The clinical characteristics of the disease can be very unspecific and make it harder to diagnose. The diagnosis is done through image criteria along with several clinical data. Treatment is described as multiple options depending on severity and availability. It is important to know the characteristics of this large-vessel vasculitis to be able to identify and treat these patients as soon as possible, the severity and prognosis can vary depending on gender, age, and ethnicity, having a worse prognosis in younger children and African patients. This chapter talks about the characteristics of this disease and how it can be different in adult patients compared to pediatrics.

2. Takayasu arteritis: review in pediatrics

Takayasu arteritis (TA) is classified as a large-vessel vasculitis. It affects the aorta and major branches by causing stenosis, occlusion, and/or aneurysms of the vessel; it is an inflammatory disease with unknown etiology. Predominantly presented in females.

Takayasu arteritis was first described by Doctor Mikito Takayasu, a Japanese ophthalmologist, after a case of changes in the retinal vessels of a 22 year old female in 1908. Since then, there have been many case reports that matched Dr. Takayasu's patient and the disease received many names like pulseless disease, aortic arch syndrome, or obstructive productive arteritis. It was until 1990 when the American College of Rheumatology published and described the disease named "Takayasu arteritis" publishing with it classification criteria for its diagnosis [1].

2.1 Epidemiology

TA is a rare disease and its frequency seems to be influenced by ethnicity. It is generally known to be presented in females under 40 years of age, but it can be seen in older patients as well as children. There is not a statistical value that is acceptable for the general population since the prevalence can vary a lot by ethnicity. TA is known to be a more popular vasculitis in Asia, and their countries have the highest prevalence. In Japan, the prevalence is higher than 4/million. In the United Kingdom, they have an incidence of 0.8/million. North America has an incidence of 2.6/million [2, 3].

Ethnicity does not only affect the incidence and prevalence of the disease, it can also affect the characteristics of presentation, the intensity of symptoms, and the prognosis of the patient. A French retrospective study compared black, white, and North African patients with TA and found that North African patients had lower survival rates in 5 and 10 years than the other two ethnicities, all because North African patients had more ischemic relapses; also white patients seem to have a prolonged diagnosis, according to the mean age of diagnosis, being 10 years later than North African and black patients [4].

The manifestation of TA can also vary, for example, Japanese patients seem to have the aortic arch and branches affected and Indian patients have abdominal aorta and branches more frequently affected [5].

2.1.1 Epidemiology in children

In children, it is very rare to see TA, and because of that there is not a lot of data, there is an estimated incidence of TA in children that is 2.6/ million of all ages. A very limited study of 21 patients in the United States found that it continues to be more common in females, having 71% of their population being females, and having a very large age gap for symptoms on set, from 1.5 months to 17 years, having a median age of 13 years old [6].

2.2 Pathogenesis

The pathogenesis of TA remains unclear, although the involvement of immune mechanisms mediated by cells that secrete proinflammatory cytokines is known to play an important role, so this leads to the use of cytokine-targeting agents, such as TNF or IL-6 inhibitors as treatment [7, 8].

Inflammatory infiltrates of the arterial wall consist of macrophages and lymphoid cells. Th1 and Th17 responses seem to play an important role as demonstrated by an increased expression of Th1 and Th17 immunity in TA, such inflammation that correlates with disease activity [8].

A possible genetic association, a polymorphism of tumor necrosis factor (TNF) has been studied and both human leukocyte antigen (HLA) classes I and II have been associated with TA, and most notably, the HLA-B52 allele has been reported across multiple ethnicities. The genetic contribution to disease pathogenesis is supported by the identification of multiple susceptibility loci in various studies. This disease was also associated with IL-6, RPS9/LILRB3, and an intergenic locus on chromosome 21q22 [7, 8].

Both the innate and adaptive immune systems seem to be involved in the pathogenesis of TA. The inflammatory process usually involves the vasa vasorum, the adventitia, and the outer part of the media and results in vessel wall damage with laminar necrosis and elastic fiber fragmentation, which is eventually replaced by fibrosis and arterial remodeling [8].

The involvement of humoral immune mechanisms is evidenced by the presence of circulating antiendothelial cell antibodies and autoantibody-producing B cells in inflammatory TA lesions that may cause vascular dysfunction. Also, TA patients have also been shown to generate a significantly large number of plasmablasts. These results lend support to the use of anti-B-cell agents in the treatment of TA [8].

2.3 Clinical presentation

TA clinical onset and clinical characteristics can be very hard to describe or identify since it is a compile of nonspecific inflammatory symptoms. We can divide TAK clinical presentation into two phases:

- Active phase or inflammatory phase, where we will have symptoms, such as fever, myalgia, weakness, arthralgias.

- Chronic phase, where it affects the aorta and branches having symptoms of ischemia.

The active phase can be very nonspecific and have different intensity of symptoms, and it seems that the active phase can be more intense in pediatric patients and have different symptoms than in adults (**Table 1**) [9].

2.4 Diagnostic criteria

The diagnosis of TA is made with specific criteria. The initial criteria created by the American College of Rheumatology (ACR) in 1990 has a sensitivity of 91% and a specificity of 98%. The diagnosis is made when the patient has three of the six diagnostic criteria. In 2009, the European Alliance of Associations for Rheumatology (EULAR) published a guide for large-vessel vasculitis, including TA, with an update in 2018. The new guides have greater sensitivity (100%) because they include a diagnostic criteria that is necessary for the diagnosis, which is an angiographic abnormality in any kind of imaging study, with greater accessibility to imaging studies nowadays the EULAR criteria is the go to criteria (**Tables 2** and **3**) [10].

Parameter	Child-onset TA	Adult-onset TA
Median age of onset (years)	14	26
Median symptom duration (months)	12	16
Pulse loss/asymmetry (%)	61.3	70.8
Systolic hypertension (%)	66.4	48.4
Vascular bruit (%)	46.2	51.9
Diastolic hypertension (%)	43.7	38.9
Claudication (%)	38.7	54.6
Malaise/fatigue (%)	33.6	31.5
Headache (%)	31.1	18.2
Fever at presentation (%)	29.4	17.4
Dyspnea (%)	23.5	25.1
Raised creatinine (%)	15.9	4.7
Weight loss (%)	10.1	13.4
Visual disturbance (%)	11.8	7.0
Syncope (%)	7.6	11.8

Table 1.
Comparison of onset symptoms in children with Takayasu arteritis (cTAK) and adults with Takayasu arteritis (aTAK) [9].

ACR diagnostic criteria for Takayasu arteritis. Diagnosis is made with three positive items
<40 years
Claudication of extremities
Decreased brachial pulse
Blood pressure difference >10 mmhg
Arteriographic abnormality
Bruit over subclavian arteries or aorta

Table 2.
ACR diagnosis criteria for Takayasu arteritis.

2.4.1 Imaging diagnosis

There are multiple imaging tools that are useful in these patients. Some are specific to make our diagnosis and others provide a complete evaluation of our patients.

The gold standard in image study is the digital subtraction arteriography since it provides a very specific view of the arteries where the caliber is measurable with more precision, as well as compares the difference in width all along the aorta and branches. Since digital subtraction arteriography is not available in every clinical center, other image studies can help with the diagnosis.

Magnetic resonance imaging (MRI) or computed angiotomography is usually more available and can also be very helpful in assessing the caliber of vessels. A contrast-enhanced MRI will allow to detect vascular abnormalities.

EULAR diagnostic criteria for Takayasu arteritis. Diagnosis is made with arteriographic abnormality plus one of the rest.
Claudication of extremities and/or decreased brachial pulse
Blood pressure difference >10 mmhg
Arteriographic abnormality*
Bruit over subclavian arteries or aorta
Hypertension systolic/diastolic blood pressure >95th percentile for height
Acute phase reactant erythrocyte sedimentation rate >20 mm per hour or C-reactive protein above normal

**obligated criteria.*

Table 3.
EULAR diagnosis criteria for Takayasu arteritis.

In patients with TA, an echocardiogram can be done to completely evaluate the cardiovascular health in our patient evaluating the ventricular function, hypertrophy, aortic valve, and aortic and coronary arteries (**Figures 1** and **2**) [11].

In the image studies, there are multiple patterns of altered anatomy in the vessel, the four principal patterns are: [13]

- Decrease of the luminal diameter.
- Total occlusion.
- Fusiform and saccular aneurysm.
- Irregular contour of the vessel.

Angiographic classification of TA classifies the image findings into five types depending on the part of the aorta that is affected: [11].

I: Branches of the aortic arch.
IIa: Ascending aorta, aortic arch, and its branches.
IIb: Ascending aorta, aortic arch, and its branches, thoracic and descending aorta.
III: Thoracic, descending aorta, abdominal aorta, and/or renal arteries.
IV: Abdominal aorta and/or renal arteries.
V: Combined features of types IIb and IV.

2.4.2 Laboratory findings

Anemia, generally hypochromic normocytic anemia, leukocytosis, and thrombocytosis have been reported in patients in an active phase of the disease or secondary to chronic inflammation [8, 14].

In pediatric cohorts, biologic inflammation is commonly reflected by the elevation of acute phase reactants, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). However, their sensitivity to reflect active disease remains uncertain, and in addition, they lack specificity as well [8].

C-reactive protein (CRP), more accurately reflects the burden of systemic inflammation and is increasingly measured as a disease activity marker, otherwise, high CRP levels have also been found to be associated with a higher risk of thrombotic complications [2, 3].

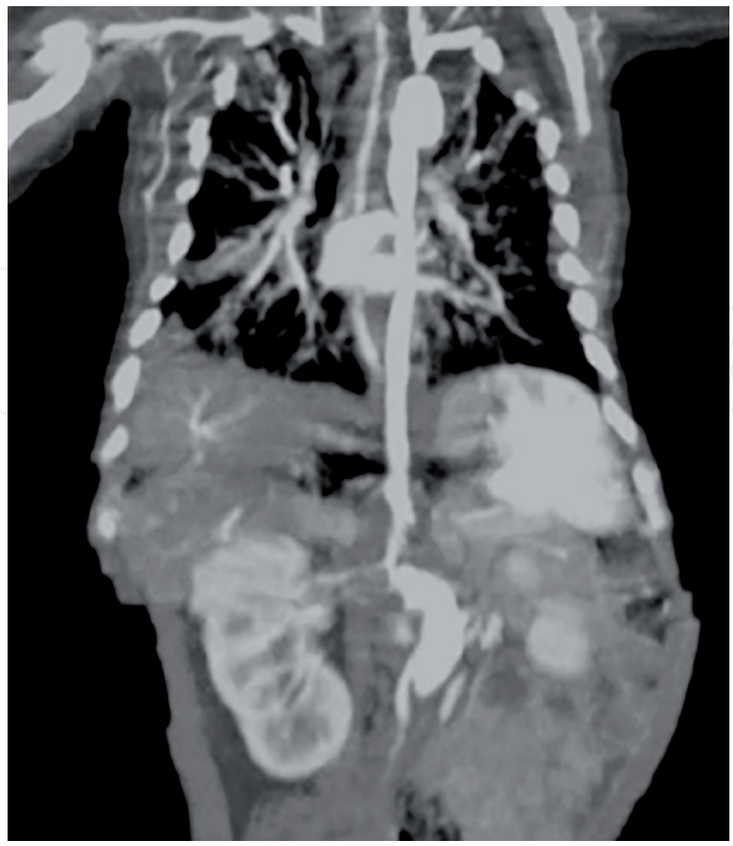

Figure 1.
Vascular abnormalities in computed tomography, such as dilation of the abdominal aorta and stenosis of the renal artery [12].

Erythrocyte sedimentation rate (ESR) increased is common in the acute phases of the disease but without clinical awareness and suspicion. ESR is more sensitive than C-reactive protein in the mentioned phases but both still have poor sensitivity and specificity, the ESR may continue to be elevated in disease remission, but actually, there are cases with active vasculitis without elevation of ESR and/or CRP [3, 7, 11].

Biomarker pentraxin-3 (PTX-3), is a protein rapidly produced in response to an inflammatory reaction, especially by endothelial cells. Levels higher than 1 ng/ml are more accurate than normal thresholds of C-reactive protein or ESR to distinguish active from inactive disease, although we need more reliable biomarkers that reflect vascular wall inflammation. PTX-3 may identify vascular progression only in a subgroup of TA patients not receiving anticytokine treatments. However, in other patients with TA, including those receiving anticytokine treatments, even plasma PTX-3 levels were shown to be normal despite ongoing smoldering vascular inflammation [2, 11].

CD8 cells with reversal of T-cell CD4:CD8 ratio increased is a marker of disease activity [11].

Some authors have suggested new biomarkers correlated with disease activity, such as matrix metalloproteinase (MMP)-2, –3, and – 9, IL-6, IFNg, vascular cell adhesion molecules (VCAM), and pentraxin-3 (PTX-3), but to date, a specific biomarker for TAK does not exist and none of them have yet been validated or implemented as a routine in clinical practice [7, 8].

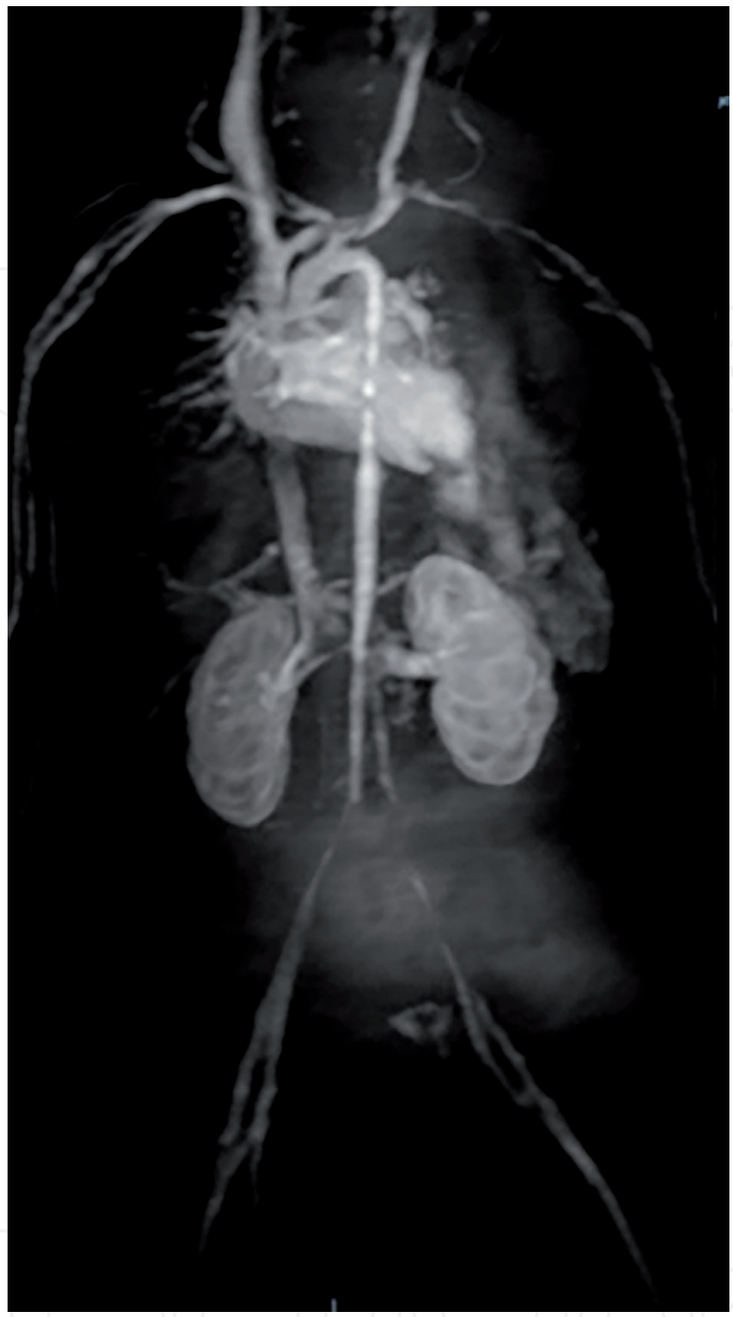

Figure 2.
Vascular abnormalities are shown in magnetic resonance angiography, such as stenosis in the thoracic aorta, iliac artery, and renal artery [12].

2.4.3 Histopathology

A lymphomonocyte infiltrate is observed, and occasionally giant cells with the presence of granulomas, which initially affect the adventitia, but progress toward the arterial lumen, in the form of panarteritis. Over time, there is a reduction in lumen due to thickening, due to fibrosis of the intima and media, thrombotic phenomena appear, and progressively, stenosis, dilation, and aneurysms [7].

A pediatric series from the United Kingdom observed lymphocytic infiltration with incipient neovascularization and the absence of granulomas. This finding contrasts with that observed in adults, in which the presence of granulomas predominates (**Table 4**) [7].

Differential diagnosis	Similar with TA	Dissimilar with TA
Giant cell arteritis (GCA) [2]	• The role of cell-mediated immunity in their pathogenesis. • Pathological findings in the vessel wall, high serum levels, and vascular expressions of cytokines (IL-6, IL-7), this is the major reason why some authors suggested that TA and GCA might exist on a spectrum within the same disease. • IL-12B is the most prominent genetic factor for both diseases.	• TA tends to affect branches of the internal carotid artery, GCA has a tendency to affect branches of the external carotid artery. • On TA, subclavian involvement tended to be asymmetric with a high frequency of left subclavian artery disease. While symmetric subclavian with concomitant axillary involvement was seen more frequently in GCA. • TA is generally seen in young females from far eastern and Asian countries, GCA is generally seen in older patients, especially of Caucasian origin. • On GCA we can find headache, jaw or tongue claudication, and scalp tenderness. • On TA, levels of Th1 cytokines are easily suppressed, and Th17 cytokines are resistant. In patients with GCA Th1 is relatively resistant and Th17 is rapidly suppressed.
Tuberculosis (TB) [2, 3]	• Granulomatous lesions. • Positive tuberculin skin test, on approximately 90% of children with TA has been observed, and about 20% of patients with TA have active tuberculosis.	• TA is associated more often with vascular stenosis, whereas tuberculosis is more often associated with erosion of the vessel wall and aneurysm development. Also, TB particularly affects the descending thoracic and abdominal aorta.

Table 4.
Similarities and differences of some differential diagnosis in comparison with Takayasu arteritis.

2.5 Differential diagnosis

Differential diagnosis are shown in **Table 4**.

2.6 Treatment options

The primary objective of treatment is inducing and maintaining remission of the disease, so early treatment is crucial to resolve or alleviate the inflammation and prevent complications and disease progression. Patient and parent's education, and cooperation between doctor and the patient (including family) are important for compliance and progression [2, 11].

The base of the treatment, at the beginning, is glucocorticoid pulses combined with immunosuppressive drugs (cyclophosphamide) to induce remission, and the use of low doses of corticosteroids and background immunosuppression as maintenance therapy (methotrexate) [7].

2.6.1 Corticosteroids

First-line treatment. Children with corticosteroid resistance should receive high-dose corticosteroids combined with another immunosuppressant agent, usually methotrexate, in order to avoid irreversible vessel damage [11].

2.6.2 Immunosuppressant drugs

Can be used in children as first or second-line agents. Has been shown to be safe and effective as a second agent to achieve sustained remission, decrease steroid dose and improve vascular lesions. This drug include methotrexate, cyclophosphamide, azathioprine, and mycophenolate mofetil [11].

2.6.3 Biological agents

More than one-half (54%) of the patients required treatment with biological agents. Antitumor necrosis factor agents (infliximab, etanercept, and adalimumab), and anti-IL-6 therapy (tocilizumab) have been used with variable effectiveness [11].

Some evidence from the case series suggests that infliximab may be effective in the management of refractory Takayasu arteritis, but has been shown to be effective in inducing and maintaining remission [7, 11].

Due to the fact that in various studies there are theories about the importance of IL-6 in the pathogenesis of this condition, such as the increase in IL-6 expression, blockade with tocilizumab has been shown to be effective in children [7].

Due to the role of Th1 and Th17 cells in the pathogenesis of the disease, there are some published cases with the use of ustekinumab (anti-IL-12/23) [7].

2.7 Prognosis in adults and children

A few studies conclude that the time lapsed from the onset of symptoms to diagnosis of the disease in a period between 2 and 11 years. The development of new drugs and the advances in surgical technology have been an important contribution to the control of disease activity but in spite of these developments, the management of childhood TA remains a challenge as diagnosis and treatment, late diagnosis and progressive disease course resistant to treatment may also cause poor prognosis. Some authors say that the worst prognosis is where patients had systemic and vascular inflammation, vascular lesions, major complications (such as retinopathy, renovascular hypertension, aortic regurgitation, and aortic aneurysm), and progressive course. Also, children under 5 years of age at the onset of the disease have a poor prognosis [2, 7, 11].

TA is associated with significant morbidity and mortality in young patients. Mortality rates vary according to several factors: geographical location, severity and extension of the lesions, treatment strategies, time of follow-up, and whether early or late series are described. Some publications show mortality rates ranging from 16 to 40%, but other ones rate mortality from 3% in the United States of America. Some common causes of death in TA include acute myocardial infarction, congestive heart failure, cerebrovascular accident, renal failure, hemorrhage, lung infection, postoperative complications, and aneurysm rupture [2, 11, 12, 15].

3. Conclusions

Takayasu arteritis continues to be a diagnostic challenge, mostly on the first-line of care, because other pathologies show similar clinical and laboratory findings and there is not a golden standard to diagnose it. In addition, the signs and symptoms are not usually the same in all patients, and it could even be an underdiagnosed disease.

On the other hand, treatment options for TA is an area in which progress has been shown in recent years. However, these options are not yet considered to be accessible to all patients.

This disease still has a field of study in terms of its pathophysiology, diagnosis, and treatment.

Acknowledgements

We would like to acknowledge Dr. Gabriel Vega for introducing us to a new field of study and allowing us to participate in the collaboration of the knowledge of Takayasu arteritis.

Conflict of interests

The authors of this chapter declare to not have a conflict of interest.

Notes/thanks

Thanks to Maria and Roberto Rivera, Daniela and Alonso Rivera, José López.

We would also like to thank our family members who motivate us to keep moving forward.

We would like to prove that women in medicine can do so much for the field and that the difficulties that we face as women every day only make us stronger.

Author details

Melisa Rivera*, Jose Heriberto López-Beltrán and Blanca Frisia Morales-López
Universidad de Guadalajara, Mexico

*Address all correspondence to: riveramelisa4@gmail.com

References

[1] Terao C. History of Takayasu arteritis and Dr. Mikito Takayasu. International Journal of Rheumatic Diseases. 2014;**17**(8):931-935

[2] Keser G, Aksu K, Direskeneli H. Takayasu arteritis: An update. Turkish Journal of Medical Science. 2018;**48**(4):681-697

[3] Brunner J, Feldman BM, Tyrrell PN, Kuemmerle-Deschner JB, Zimmerhackl LB, Gassner I, et al. Takayasu arteritis in children and adolescents. Rheumatology (Oxford, England). 2010;**49**(10):1806-1814

[4] Arnaud L, Haroche J, Limal N, Toledano D, Gambotti L, Chalumeau NC, et al. Takayasu arteritis in France: A single-center retrospective study of 82 cases comparing white, North African, and black patients. Medicine. 2010;**89**:1-17

[5] Moriwaki R, Noda M, Yajima M, et al. Clinical manifestations of Takayasu arteritis in India and Japan – New classification of angiographic findings. Angiology. 1997;**48**:369-379

[6] Szugye HS, Zeft AS, Spalding SJ. Takayasu arteritis in the pediatric population: A contemporary United States-based single center cohort. Pediatric Rheumatology Online Journal. 2014;**12**:21

[7] Lacruz L, Mir M. Arteritis de Takayasu. Protoc diagn ter pediatr. 2020;**2**:259-269

[8] Aeschlimann F, Twilt M, Yeung R. Childhood-onset Takayasu Arteritis. European Journal of Rheumatology. 2020;**7**(Suppl. 1):S58-S66

[9] Danda D, Goel R, Joseph G, Kumar ST, Nair A, Ravindran R, et al. Clinical course of 602 patients with Takayasu's arteritis: Comparison between childhood-onset versus adult onset disease. Rheumatology (Oxford, England). 2021;**60**(5):2246-2255

[10] 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. Annals of the Rheumatic Diseases. 2010;**69**:798-806

[11] Di Santo M, Stelmaszewski EV. Takayasu arteritis in paediatrics. Cardiology in the Young. 2017;**28**(03): 354-361

[12] Vega-Cornejo G, Rivera M, Bañuelos-Zapata J. Case Report: Takayasu Arteritis in a new born, five years follow-up. Revista colombiana de Reumatologia. 2021 [Online]

[13] Hyung PJ. Conventional and CT angiographic diagnosis of Takayasu Arteritis. International Journal of Cardiology. 1996;**54**(Suppl):S135-S141

[14] Dammacco F, Cirulli A, Simeone A, et al. Takayasu arteritis: A cohort of Italian patients and recent pathogenetic and therapeutic advances. Clinical and Experimental Medicine. 2021;**21**:49-62

[15] Seyahi E. Takayasu arteritis: An update. Current Opinion in Rheumatology. 2017;**29**:51-56