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## **Takayasu's arteritis in children – a review**

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### **Abstract**

Takayasu's arteritis is an inflammatory disease of unknown origin involving aorta, its primary branches and pulmonary artery. This article briefly reviews the pathology, clinical features and treatment of Takayasu's arteritis, focusing mainly on the disease in children.

**MeSH:** Takayasu's arteritis, Aortoarteritis, Vasculitis, Heart failure, Angioplasty

## Introduction

Takayasu's arteritis is a chronic inflammatory disease that involves the aorta, its branches and the pulmonary arteries<sup>1–5</sup>. The inflammation results in varying degree of stenosis, occlusion or dilatation of the involved vessels. The aetiology and the precise pathogenesis of Takayasu's arteritis are still unknown but much has been learnt about the disease since its initial description by M. Takayasu, a Japanese ophthalmologist in 1908.<sup>6</sup> This article reviews the salient features of Takayasu's arteritis, especially as seen in children.

## Epidemiology

Takayasu's arteritis is recognised world-wide, although it is commoner in south-east Asia, Africa and south America.<sup>7</sup> This disease is the commonest cause of renovascular hypertension in Asian children,<sup>8</sup> but exact prevalence data is not available. A systematic survey in Japan during 1982-84 revealed 2,600 patients of Takayasu's arteritis,<sup>9</sup> and the incidence was estimated at 2.6 per million persons/year in USA<sup>10</sup> and 1.2 per million persons/year in Sweden in hospital based studies.<sup>11</sup>

Takayasu's arteritis is predominantly a disease of young adults in the second and third decades of life. The onset of illness may be earlier, including in childhood<sup>12,13</sup> but rarely in infancy.<sup>14</sup> The female:male ratio has varied from 9:1 in reports from Japan<sup>9</sup> to 1.3:1 in India.<sup>15</sup> The female preponderance is less obvious in children.<sup>15–17</sup> Interestingly, the pattern of vessel involvement in Takayasu's arteritis also varies in different parts of the world.<sup>18</sup> The involvement of the aortic arch and its branches is common in Japan, whereas the thoracoabdominal aorta is mainly involved in patients from Korea and India. It is not known whether this variation reflects differing causes of Takayasu's arteritis. Racial variation also occurs as the disease is uncommon in Caucasians. Moreover, in Israel, Takayasu's arteritis is seen in Sephardic Jews but not in Ashkanazi Jews.<sup>9</sup>

Genetic susceptibility to Takayasu's arteritis has been extensively studied. There are heterogeneous population data regarding HLA associations in TA. HLA B-52 and DR-2 are associated with Takayasu's arteritis in Japan,<sup>19</sup> HLAB-52 and B-5 association is also reported from Korea and India,<sup>18</sup> whereas HLA B-39 is frequently found in Mexican Takayasu's arteritis patients.<sup>20</sup> Further characterisation of HLA association in Takayasu's arteritis is being studied in order to identify alleles or epitopes responsible for the susceptibility to this disease.<sup>20,21</sup>

## Histopathology

TA involves mainly the elastic arteries.<sup>1,22,23</sup> The disease may be patchy with normal skip areas in between, or diffuse along the length of the entire vessel. In the initial acute stage of the disease, exudative and granulomatous inflammation is seen, whereas fibrosis predominates later, but the two stages may co-exist.<sup>23</sup> The initial site of inflammation is around vasa vasorum in the media and the adventitia. Mononuclear cell infiltration predominates and granulomas with giant cells (epithelioid or foreign body type) are seen.

Fragmentation of elastic fibres (elasticophagia) is prominent.<sup>23</sup> Destruction of the smooth muscle cells in the media leads to weakening of the vessel wall and dilatation. Deposition of ground substance rich in acid mucopolysaccharide and reactive fibrosis occurs in the intima at the site of medial inflammation.<sup>22</sup> Later in the disease process, nodular fibrosis in all layers of the artery is seen and the intima may become several times thicker than media (Figure 1) obliterating the lumen. Rapid or more severe inflammation leads to vessel dilatation and aneurysm formation, but stenosis and occlusions are more common. Thromboses in stenosed arteries are sometimes seen. The corresponding organ shows ischaemic changes, and this ischaemia largely determines the clinical features of the disease.

### **Pathogenesis**

The exact pathogenesis of Takayasu's arteritis is unknown. Its relationship to tuberculosis has long been debated.<sup>24</sup> Takayasu's arteritis is more common in the parts of the world with high incidence of tuberculosis, but exceptions like Japan are intriguing.<sup>25</sup> Case reports of occurrence of Takayasu's arteritis with rheumatoid arthritis,<sup>3</sup> ulcerative colitis,<sup>26</sup> systemic lupus,<sup>27</sup> Crohn's disease,<sup>28</sup> sarcoidosis<sup>12,29</sup> amyloidosis<sup>30</sup> etc, although sporadic, may indicate immune mechanisms in the pathogenesis. Relatively little information about the disease in the acute stage is available. Aetiopathogenesis may not be obvious by studying the chronic phase of the disease, as in rheumatic heart disease. Evidence from the study of lesions in the active phase suggests that inflammation results from cell mediated immune responses.<sup>31</sup> A number of lymphocytes ( $\alpha\beta$ -T-cells,  $\gamma\delta$  T cells and natural killer cells) infiltrate and incite the damage by liberating perforin on to arterial tissue. Further characterisation of T-cells receptors suggests that these cells are reactive to particular antigen/s.<sup>31</sup> The exact antigens involved remain unknown. However, evidence is mounting that heat shock protein(HSP)-65 may be one of the important antigens. HSP-65 is a major antigen of mycobacterium tuberculosis, BCG and many other bacterial species as well as synthesised by tissues in response to stress.<sup>32</sup> Cross reactivity and sequence homology between HSP-65 and HLA class II molecules has been described.<sup>32</sup> Moreover, expression of HSP-65, HLA class I and II antigens is also markedly increased in affected aortic tissue.<sup>31</sup> Thus, genetically linked immune responses to unidentified antigen may incite autoimmune damage by cell mediated pathways, and may result in the disease and relapses. A detailed discussion on immunopathogenesis of Takayasu's arteritis has recently been published.<sup>32</sup>

### **Diagnosis**

The criteria for the diagnosis of Takayasu's arteritis as suggested by Ishikawa<sup>33</sup> are shown in Table 1. The criteria adopted by the American College of Rheumatology are shown in Table 2.<sup>34</sup> None of the diagnostic criteria are entirely satisfactory, but the clinical diagnosis in the proper context is seldom difficult. Essentially, the diagnosis depends on the typical angiographic morphology, history or presence of constitutional symptoms suggestive of a systemic illness, and the differential diagnosis of other, similar conditions such as other causes of inflammatory aortitis (e.g. syphilis,

tuberculosis, giant cell arteritis, Buerger's, Behcet's, Cogan and Kawasaki diseases, spondyloarthropathies), developmental abnormalities (e.g. Ehlers-Danlos syndrome, Marfan's syndrome) Other aortic abnormalities such as neurofibromatosis, ergotism and radiation fibrosis need to be excluded.<sup>12</sup> Atherosclerosis of aorta is distinguished on clinical and morphological grounds, but secondary atherosclerotic changes may occur in older patients with Takayasu's arteritis.

### Angiographic morphology

Conventional or digital subtraction angiography has been considered the gold standard for the diagnosis of Takayasu's arteritis. Angiography shows luminal irregularity, vessel stenosis, occlusion, dilatation or aneurysms in the aorta or its primary branches.

Neurofibromatosis of the abdominal aorta and some other causes of mid-aortic syndrome may produce an identical angiographic picture in children.<sup>35</sup>

Based on angiographic morphology, Takayasu's arteritis is divided into type I (involving aortic arch and its branches), type II (thoracoabdominal aorta and its branches) and type III (involving lesions of both type I & II) (Figures 2,3). Involvement of pulmonary arteries in addition to any of the above types is grouped as type IV.<sup>4,12</sup>

Involvement of the left and right subclavian arteries is very common in Takayasu's arteritis. Thoracoabdominal aortic involvement is commoner (type II/III) in children.<sup>15-17</sup> The infrarenal aorta or the iliac vessels are not usually involved in Takayasu's arteritis. Similarly, the inferior mesenteric artery is rarely involved. Unlike coarctation of the aorta, intercostal collaterals rarely occur as the diffuse intimal disease in the aorta also involves the ostia of these intercostal vessels (Figure 4). Aortic intimal calcification may be seen.

Figure 1 Pathology in the chronic phase of Takayasu's arteritis showing fibrosis in all the layers of the vessel wall and markedly thickened intima (arrow)



Table 1 Ishikawa's criteria for the clinical diagnosis of Takayasu's disease

Criteria*	Definition
<b>Obligatory criteria</b>	
Age <40 year	Age < 40 year at diagnosis or at onset of "characteristic signs and symptoms" of one month duration in patient history.
<b>Two major criteria</b>	
Left mid subclavian artery	The most severe stenosis or occlusion present in the mid portion from the point one cm proximal to the left vertebral artery orifice to that three cm distal to the orifice determined by angiography.
Right mid subclavian artery lesion	The most severe stenosis or occlusion present in the mid portion from the right vertebral artery orifice to the point 3 cm distal to the orifice determined by angiography.
<b>Nine minor criteria</b>	
High ESR	Unexplained persistent high ESR>20 mm/h (Westergren) at diagnosis or presence of evidence in patient history.
Carotid artery tenderness	Unilateral or bilateral tenderness of common carotid arteries by physician palpation; neck muscle tenderness is unacceptable.
Hypertension	Persistent blood pressure 140/90mmHg brachial or > 160/90mmHg popliteal at age <40 year. Or presence of the history at age <40 year.
Aortic regurgitation or annuloaortic ectasia	By auscultation or Doppler echocardiography or angiography
Pulmonary artery lesions	By angiography or two dimensional echocardiography. Lobar or segmental arterial occlusion or equivalent determined by angiography or perfusion scintigraphy; or presence of stenosis, aneurysm, luminal irregularity or any combination in pulmonary trunk or in unilateral or bilateral pulmonary arteries determined by angiography.
Left mid common carotid lesion	Presence of the most severe stenosis or occlusion in the mid portion of 5cm in length from the point 2 cm distal to its orifice determined by angiography.
Distal brachiocephalic trunk lesion	Presence of the most severe stenosis or occlusion in the distal third lesion determined by angiography.
Descending thoracic aorta lesion	Narrowing, dilatation or aneurysm, luminal irregularity or any lesion combination determined by angiography; tortuosity alone is unacceptable.
Abdominal aorta lesion	Narrowing, dilation or aneurysm, luminal irregularity or any combination and absence of lesion in aorto-iliac region consisting of 2cm of terminal aorta and bilateral common iliac arteries determined by angiography; tortuosity alone is unacceptable.

\* The proposed criteria consist of one obligatory criterion, two major criteria and nine minor criteria. In addition to the obligatory criterion, the presence of two major criteria, or one major and two or more minor criteria or four more minor criteria suggests a high probability of the presence of Takayasu's disease.

Table 21990 criteria of American College of Rheumatology for the classification of Takayasu arteritis

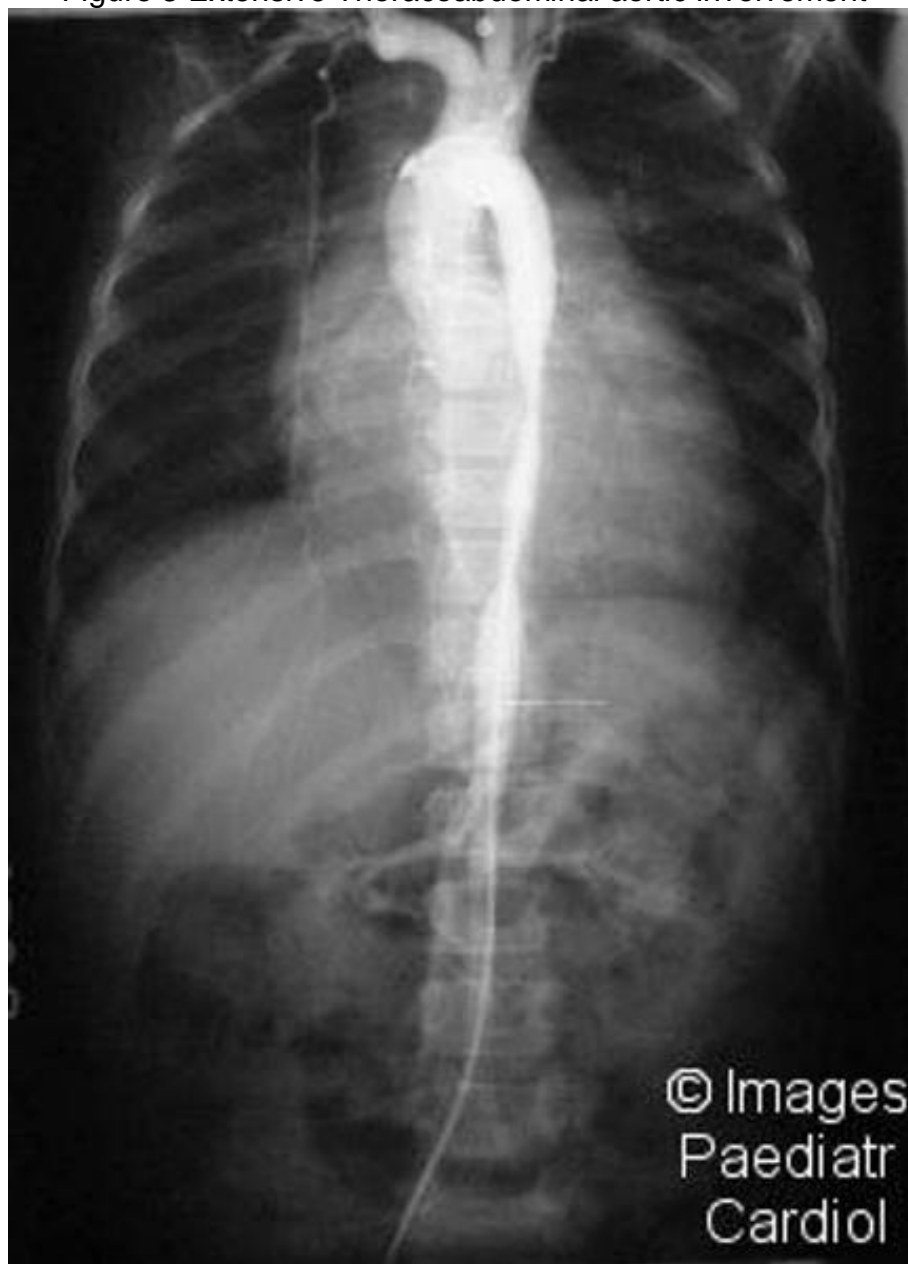
Criteria	Definition
Age at disease onset in year	Development of symptoms or findings related to Takayasu arteritis at age <40 years.
Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of one or more extremity while in use, especially the upper extremities.
Decreased brachial artery pulse	Decreased pulsation of one or both brachial arteries
BP difference >10mmHg	Difference of >10mmHg in systolic blood pressure between arms
Bruit over subclavian arteries or aorta	Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta
Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due arteriosclerosis, fibro-muscular dysplasia, or similar causes: changes usually focal or segmental

*Takayasu arteritis is diagnosed if at least three of six criteria are present*

Figure 2 Severe type I arteritis with complete occlusion of left carotid and subclavian artery. The right subclavian artery is also occluded



Figure 3 Extensive Thoracoabdominal aortic involvement



Saccular or fusiform aneurysms of the aorta occur in 2-26% of cases, and usually coexist with stenotic lesions.<sup>36,37</sup> Aneurysms without stenosis occur in 1-2% of cases.<sup>36</sup> Pseudoaneurysm or dissection of the aorta are extremely rare.<sup>23</sup>

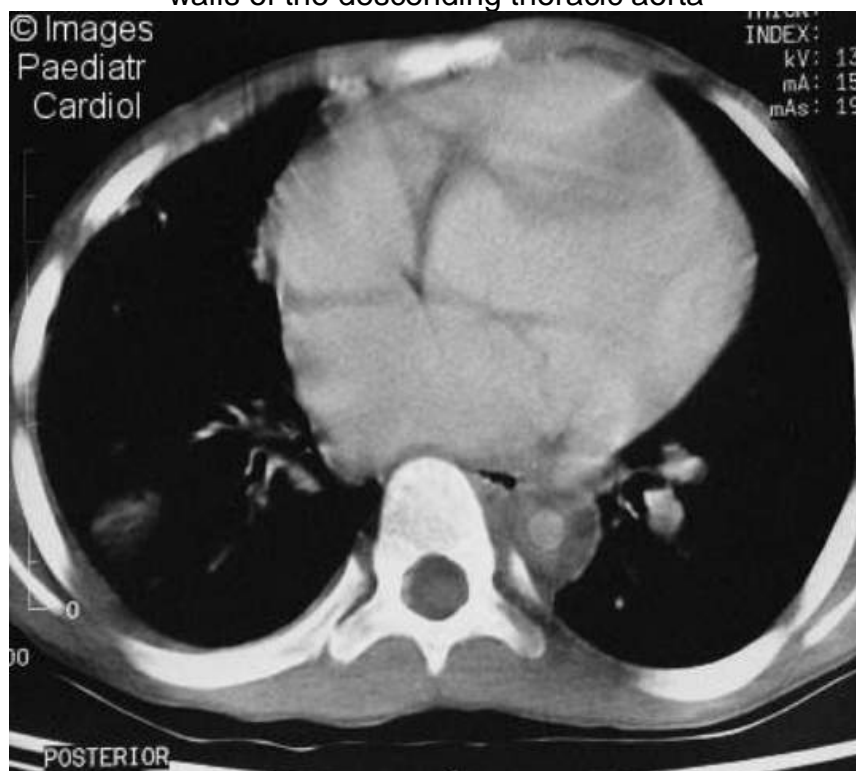
The angiographic features reflect only the luminal aspects of inflammation and occur relatively late in the course of the disease. More recently, cross-sectional imaging with helical computerised tomography,<sup>38</sup> ultrasound<sup>39</sup> or contrast enhanced magnetic resonance imaging<sup>40</sup> provide information on mural changes of the vessels. computerised tomography scan may reveal aortic wall thickness (Figure 5) and aortic calcification, helical computerised tomography angiography may show enhancement of thickened aortic wall with inflammation. Similarly, T1-weighted contrast enhanced magnetic

resonance imaging also depicts wall thickness and its enhancement with activity of the disease. These noninvasive modalities may replace angiography for the diagnosis, and for monitoring therapy and progression of the disease.

Figure 4 The disease in a 4-year old child. Note the diffuse involvement of descending aorta and paucity of collaterals



Figure 5 Contrast enhanced CT scan showing concentric, thickened aortic walls of the descending thoracic aorta





## Clinical features

Takayasu's arteritis has an early active inflammatory phase and a late chronic, but many patients do not give a history suggestive of previous inflammatory illness. The active phase of the illness lasts for weeks to months, and may have a remitting and relapsing course. Constitutional symptoms like fever, anorexia, loss of weight, night sweats, arthralgia, skin rash etc. may occur during the active phase but the correct diagnosis of Takayasu's arteritis is seldom made in the early phase. Evidence of vessel inflammation such as tenderness along arteries, bruits and aneurysm may point to the diagnosis of Takayasu's arteritis. The clinical features in three large series from different parts of the world are shown in table 3. Systemic symptoms are seen in a high proportion of children with Takayasu's arteritis. The usual presenting symptoms are due to hypertension, heart failure or a neurological event. Claudication, bruit or a missing pulse in an asymptomatic child are other uncommon presentations. Children with Takayasu's arteritis have higher morbidity and mortality than adults.<sup>15,16</sup>

Table 3 Takayasu's arteritis in children

	Mexico <sup>16</sup>	India <sup>15</sup>	South Africa <sup>17</sup>
N	55	47	31
Age (Mean) years	<15(6)	4-15	2.4-14.5 (8.4)
Female : Male	3.5:1	1.35:1	1.4:1
Constitutional symptoms (%)	65	44	6
Hypertension (%)	89	72	78
Heart failure (%)	64	64	60
Neurological symptoms (%)	54	40	21
Increased ESR(%)	71	59	70
Angiographic morphology Type II/III(%)	n/a	100	66
Renal art stenosis (%)	n/a	74	78
Mortality (%)	31	10	21

Hypertension in Takayasu's arteritis results from renal artery stenosis or aortic narrowing and aortic fibrosis. It is often severe and may cause hypertensive encephalopathy or heart failure. Takayasu's arteritis is the commonest cause of renovascular hypertension in Asian children. The diagnosis of Takayasu's arteritis may be suggested by a missing pulse or a renal or aortic bruit. However, these are not universal. The diagnosis of hypertension may be entirely missed if all the peripheral pulses are not carefully examined. Renal arterial stenosis may be bilateral and usually coexists with aortic involvement<sup>41,42</sup> (Figure 6). The ostia of the renal arteries are commonly involved, but the intrarenal vasculature and small vessels are generally normal. Therefore the use of ACE inhibitors in Takayasu's arteritis needs to be carefully considered and such drugs preferably started only after obtaining an aortogram.<sup>43</sup>

Heart failure from Takayasu's arteritis is common in children (Table 3) and is an important cause of mortality. Hypertension is the most common reason for heart failure, but may occur in the absence of severe hypertension.<sup>15</sup> Myocarditis, coronary arterial involvement, organic valvar involvement, or pulmonary artery involvement may cause or contribute to the heart failure.

Frequently, children with heart failure and Takayasu's arteritis are misdiagnosed as having dilated cardiomyopathy as the echocardiogram shows systolic ventricular dysfunction and hypertension may be missed. Mild hypertension in the presence of severe heart failure, left ventricular hypertrophy on echocardiogram, or a dilated aorta may point to the correct diagnosis.

Familiarity with the disease may suggest the correct diagnosis, even when no obvious pointers are present. Half of the children with heart failure have mitral regurgitation and rheumatic heart disease may be falsely diagnosed.<sup>15</sup> Aortic regurgitation from a dilated aorta is rarely seen in children. Treatment of hypertension or aortic obstruction ameliorates the heart failure in the majority of children. However, heart failure in the absence of hypertension suggests myocarditis as a cause for ventricular dysfunction. Myocarditis in Takayasu's arteritis is rare and may respond to immunosuppressive treatment.<sup>44</sup>

Figure 6 Digital subtraction angiogram of a 9-year old boy showing bilateral renal arterial stenosis and severe perirenal aortic narrowing



Coronary arterial involvement in Takayasu's arteritis is usually ostial and proximal (Figure 7), but diffuse lesions or arteritis and aneurysm rarely

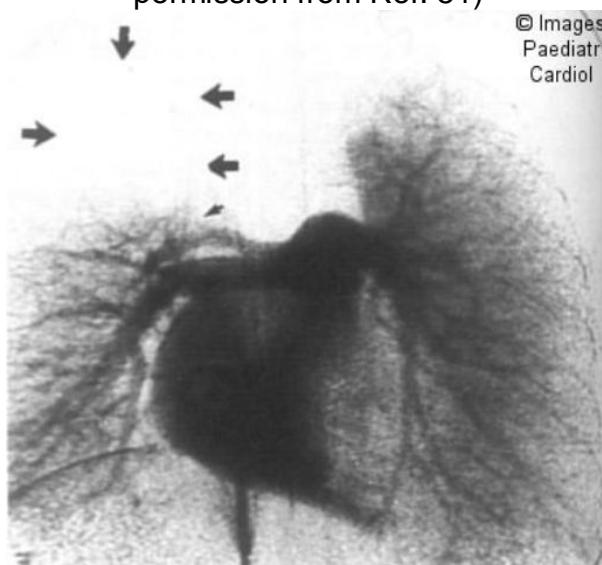
occur.<sup>45,46</sup> About 10% of adult patients with Takayasu's arteritis have coronary arterial involvement but the incidence in children has not been studied. Coronary arterial involvement may cause myocardial infarction,<sup>47</sup> angina or heart failure and may necessitate angioplasty, or surgical treatment even in children.<sup>48,49</sup>

Pulmonary arterial involvement has been found in nearly 70% of the patients on angiographic studies<sup>50,51</sup>, but is usually mild. Pulmonary artery involvement correlates with extensive aortic involvement<sup>50</sup> but pulmonary arterial involvement as the only lesion or as presenting manifestation of disease is also described.<sup>52</sup> The disease involves segmental and subsegmental branches, more in the upper lobes but larger branches may be involved (Figure 8). The angiographic picture may closely mimic thromboembolism. A history of haemoptysis, chest pain, disproportionate pulmonary arterial hypertension, or abnormal ventilation-perfusion scan<sup>53</sup> may suggest pulmonary involvement. Response of pulmonary arterial lesions to therapy has not been well studied.

Figure 7 Left main coronary arterial narrowing in a 16 year old girl with Takayasu's arteritis (Reproduced with permission from Ref. 46)



Figure 8 Pulmonary arterial involvement in a young child (Reproduced with permission from Ref. 51)



Neurological symptoms such as headache, visual disturbances and amaurosis fugax are common in Takayasu's arteritis. Syncope and transient ischaemic attacks may occur due to severe carotid or vertebral artery stenosis. In children, cerebrovascular accidents are often secondary to severe hypertension and its complications. Hypertensive retinopathy is commoner than ischemic retinopathy in Takayasu's arteritis.<sup>54</sup> Type I Takayasu's arteritis involving the aortic arch and its branches is uncommon in children (Table 3).

### Assessment of disease activity

The presence of systemic symptoms, raised ESR and worsening of vessel stenosis are considered evidence of active disease (Table 4).<sup>12</sup> However, histological evidence of disease have been observed in clinically inactive disease,<sup>55</sup> and angiographic progression of disease has occurred in the absence of clinically active disease.<sup>12</sup> Recent advances in noninvasive imaging may assist in identifying active inflammation.<sup>38,40</sup>

Interestingly, raised interleukin-6 and RANTES have been reported to correlate with the disease activity, and may prove useful in the monitoring of therapy.<sup>56</sup>

Table 4 Criteria for Active Disease in Patients with Takayasu Arteritis<sup>12</sup>

Constitutional features, such as fever, musculoskeletal pain (no other cause identified)
Elevated erythrocyte sedimentation rate (>20 mm / hr)
Features of vascular ischemia or inflammation, such as claudication, diminished or absent pulse, bruit, vascular pain (carotodynia), asymmetric blood pressure in either upper or lower limbs (or both)
Typical angiographic features.

*New onset or worsening of two or more features indicates "active disease".*

## Treatment

In the acute phase of TA, treatment with corticosteroids (1mg/kg/d) leads to clinical remission in 60% of cases.<sup>12</sup> Immunosuppression with cyclophosphamide (1-2mg/kg/d), azathioprin (1-2mg/kg/d) or methotrexate (0.15-0.35 mg/kg/week) may be tried in resistant cases, or in order to reduce steroid dosages.<sup>12</sup> The duration of treatment varies empirically on clinical assessment of activity. Median duration to remission was 11 months in children in one series,<sup>12</sup> but there are, to date, no large studies involving children. Rare instances of reappearance of pulses or a reduction in renal artery stenosis with steroid treatment have been reported.<sup>57,58</sup> The major morbidity and mortality of Takayasu's arteritis results from stenosis and occlusion of the aorta, renal and carotid arteries. Balloon dilatation of stenosed segments has revolutionised the treatment of Takayasu's arteritis. Percutaneous transluminal renal arterial dilatation (PTRA) is successful in up to 90% of cases<sup>41,42</sup> and blood pressure control is achieved in 60% (Figure 9). Restenosis may occur in 20-25% cases. Renal artery stents are not usually required. Balloon dilatation is preferably done in the chronic phase of disease, but successful dilatation may be done during acute phase of Takayasu's arteritis, if required (unpublished observation). Similarly, balloon dilatation of aortic narrowing is highly effective even in diffuse, long segment stenoses (Figure 10).

Close to 90% success rates have been reported for aortic angioplasty in children.<sup>59,60</sup> Restenosis may occur in 14-20% at follow-up. Suboptimal results may be observed in long segment stenosis but clinical benefits usually occurs even with these. Remarkable recovery from heart failure follows successful dilatation<sup>59,60</sup> (Figure 11). The use of stents in children with Takayasu's arteritis is discouraged and small dissecting flaps may heal well. However, stents have also been successfully used to treat occlusive dissecting flaps, or aortic obstruction.<sup>61</sup> Interventional treatment of carotid stenosis, although uncommonly involved in children, is also feasible.<sup>62</sup> Because of the diffuse, inflammatory and possibly progressive nature of the disease, surgical treatment is not preferred for Takayasu's arteritis except for undilatable symptomatic stenotic lesions and for large aneurysms.<sup>63</sup>

Figure 9 Percutaneous transluminal renal arterial dilatation of bilateral renal artery stenosis in a child (a) before and (b) after dilatation

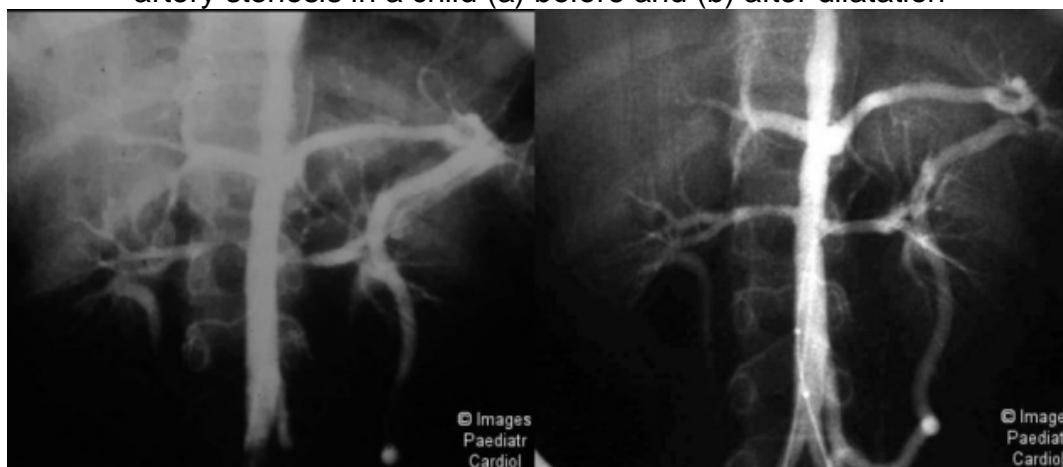
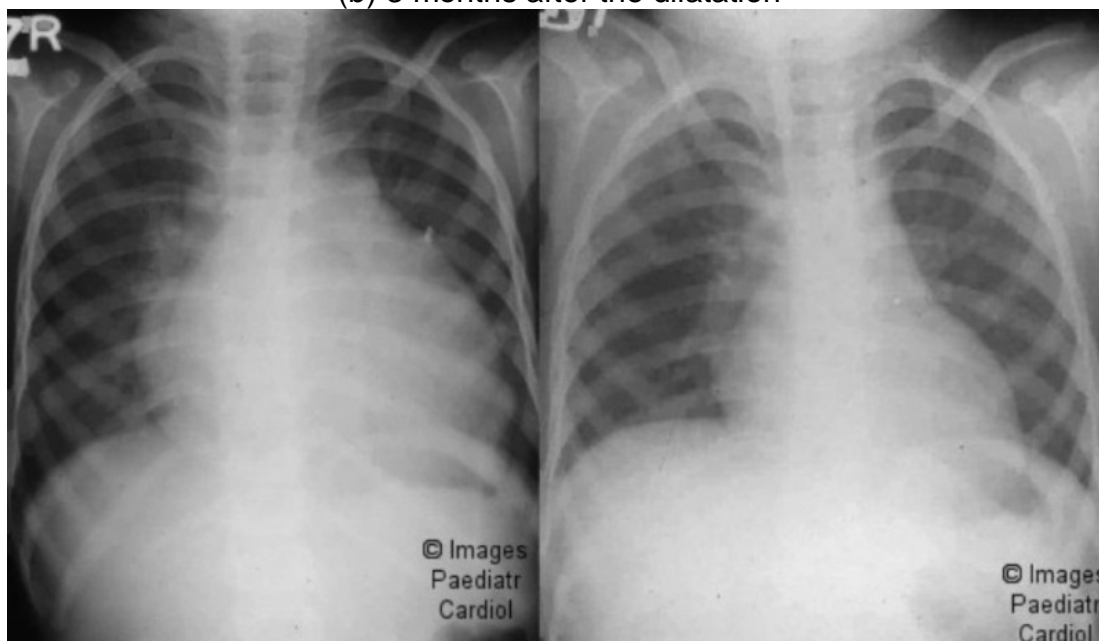


Figure 10 Balloon dilatation of severe, long segment aortic narrowing (a) before and (b) after the dilatation



Figure 11 The chest x-rays of the same patient as in figure 10. (a) before, and (b) 3 months after the dilatation

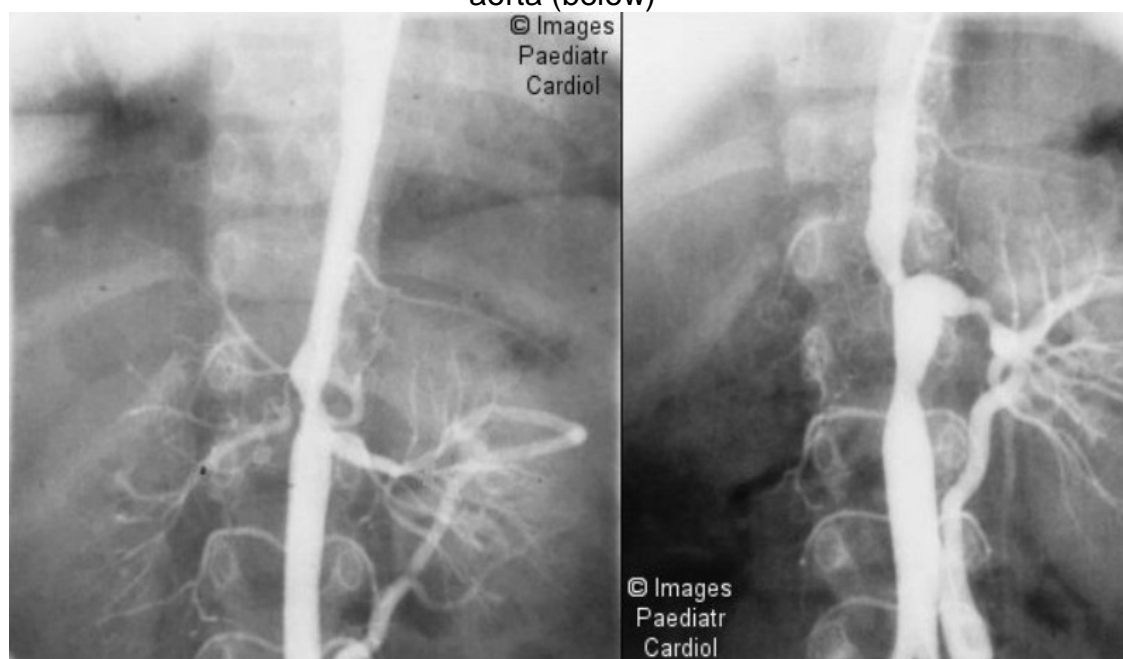


## Prognosis

Takayasu's arteritis in children is a serious illness and a mortality of 10-30% has been reported on followup.<sup>15-17</sup> More recently, the prognosis has significantly improved due to interventional procedures for the treatment of renal and aortic stenosis. Long term follow up data on children is not available. In a study of 88 adults with Takayasu's arteritis, 5 and 10 year survival after the onset of disease was 91% and 84% respectively.<sup>64</sup> The presence of severe Takayasu's arteritis (defined as the presence of severe grades of hypertension, aortic regurgitation, retinopathy, or aneurysms), poor functional class or cardiac involvement, predicted a poorer outcome. A relatively stable course is anticipated in the absence of severe complications. Successful pregnancies have been reported in patients with Takayasu's arteritis.<sup>65</sup> Chronic, burnt out lesions of Takayasu's arteritis remain stable for years. In an angiographic study, after a seven year followup, the lesions remained stable in 80% of patients.<sup>66</sup> However, the progression of lesions even in the absence of obvious clinical activity has also been described (Figure 12).<sup>12</sup>

Clearly, much remains to be learnt about Takayasu's arteritis. This enigmatic disease still remains a challenge.

Figure 12 The progression of the disease over 1 year in a young boy. Note the development of renal artery aneurysm and disease involving the infrarenal aorta (below)



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