Takayasu’s Arteritis: A Review Article

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Author’s contribution

This work was carried out by one author. Author JAB performed the literature and wrote the manuscript. He approved the final manuscript.

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ABSTRACT

We selected the medicine research papers in English language published from the year 2005 to the date to determine the clinical significance of Takayasu’s arteritis (TA) and to review the literature available on this condition. TA is a world-wide, chronic inflammatory disease of unknown etiology. It is more prevalent in Asian countries. There are no specific laboratory tests to diagnose TA as it usually presents with non-specific symptoms such as fatigue, fever, arthralgia, weight loss, malaise, weakness and vision changes. Angiographic imaging is considered to be the gold standard investigation in diagnosing TA. Steroids with subsequent tapering doses are the mainstay of medical treatment; however, for addressing the refractory cases additional therapy becomes necessary. Reconstructive vascular surgery is limited to the severe and irreversible stenotic lesions where surgery becomes inevitable.

Keywords: Takayasu’s arteritis; TA; Takayasu’s arteritis in women; takayasu’s arteritis in children; diagnosis; treatment.

1. LITERATURE REVIEW

We collected all possible literature by conducting a medical search on Takayasu’s arteritis (TA) in the search engines (e.g. Google, Yahoo, Bing) in English language. The keywords like Takayasu arteritis, Takayasu disease, Takayasu arteritis in women, Takayasu arteritis in children, diagnosis of Takayasu arteritis and treatment of Takayasu arteritis and combination

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of the keywords were used to search the current and related literature. We included peer-reviewed articles and case studies published in authorized medical journals, and the content published in the recent editions of reference books.

1.1 Epidemiology

TA has world-wide distribution, but prevalent in Asian populations [1,2]. It was first reported in 1908 by Japanese ophthalmologists [3,4]. Clinical pattern of the disease in Greece resembles the pattern observed in Japan and Western countries [5,6]. However, aortic arch involvement has been reported more in Japanese while the involvement of abdominal aorta is more in Indian and Korean patients [7]. TA is seen predominantly in young women (female: male ratio 8:1) with a typical onset at the age of 25-30 years [1-10]. Some hospital-based studies reflect the incidence of 1-2 cases per million [11], however available data on incidence and prevalence is yet limited. TA is the commonest cause of renovascular hypertension in India [12]. Also, a study in Italy reveals that aortic aneurysm is not rare in the patients with TA [13].

1.2 Etiology and Pathogenesis

The etiology of TA is still not known [1,8,14,15]. Similarly, exact pathogenic sequence of the disease is yet to be established [16]. However, a hypothesis has been developed where 65kDa heat-shock protein in the aortic tissue gets stimulated by unknown stimulus leading to the induction of major histocompatibility class I chain-related A (MICA) located on the vascular cells [16].

TA is a chronic granulomatous panarteritis of large sized arteries, classically involving the aortic arch, but one third of the cases also affect the remainder of the aorta and its branches, and pulmonary arteries [2,8]. The gross morphologic examination, in most of the cases, irregular thickening of the aortic and its branch vessel wall with intimal wrinkling is seen [1,8,17]. When aortic arch is involved, the orifices of aortic branch vessels to the upper portion of the body may be markedly narrowed or even obliterated. The coronary and renal arteries may be equally affected. Histological findings may range from an adventitial mononuclear infiltrate with perivascular cuffing of the vasa vasorum (channels supplying blood vessels) to marked mononuclear inflammation the media [18,19]. Sometimes, it becomes difficult to distinguish between granulomatous inflammation of TA and that of temporal arteritis, especially when it is abundant with giant cells and patchy necrosis [8]. Thus, the difference between TA and temporal arteritis largely depends upon the age of the patient and most of the giant cell lesions of the aorta in young patients are rendered as those of TA [8,20]. Along the course of TA or after treatment with steroids collagenous fibrosis involving all layers of the vessel wall occurs. The lymphocytic infiltration also accompanies the collagenous fibrosis. Aortic root involvement may lead to dilatation and aortic valve insufficiency [1,21]. Myocardial infarction may result in narrowing of coronary ostia [8,22].

1.3 Clinical Manifestations

TA consists of an early active phase and a late chronic phase; however some cases may not be suggestive of previous inflammatory history. The active phase may last for weeks to months and may have remitting and relapsing pattern [22]. The patients with TA usually present with claudication and non-specific systemic symptoms like fatigue, fever, arthralgia, weight loss, malaise, weakness, night sweats and vision changes [1,23,24]. The salient
clinical features markedly lower blood pressure and weaker pulses in the upper extremities with coldness or numbness of the fingers [8,25,26]. This is why TA is also named as a “Pulseless Disease”. On examination, peripheral pulses of the upper extremities (e.g. radial pulses) are often found week or even absent. Visual disturbances like visual defects, retinal hemorrhages and total blindness are also common in TA [8,22]. Neurological deficits and cerebral aneurysm have been reported in children with TA [8,27]. Bicakcigil, et al. (2009) studied 248 cases of TA and came across the features mentioned in the Table-1 [6].

### Table 1. Features of TA

<table>
<thead>
<tr>
<th>Features</th>
<th>Percentage</th>
<th>Features</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Constitutional symptoms</td>
<td>66%</td>
<td>Hypertension</td>
<td>43%</td>
</tr>
<tr>
<td>Diminished pulses</td>
<td>88%</td>
<td>Aortic regurgitation</td>
<td>33%</td>
</tr>
<tr>
<td>Bruits</td>
<td>77%</td>
<td>Renal artery stenosis</td>
<td>26%</td>
</tr>
<tr>
<td>Pain in extremities</td>
<td>69%</td>
<td>Cerebrovascular accidents</td>
<td>18%</td>
</tr>
<tr>
<td>Claudication</td>
<td>48%</td>
<td>Pulmonary hypertension</td>
<td>12%</td>
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Involvement of the distal aorta and pulmonary arteries cause claudication of the legs and lead to pulmonary hypertension [8,28,29]. However, pulmonary hypertension is a rare manifestation of TA. Some studies bring to light that patients with TA may have loud S₂ at base and systolic bruit at supraclavicular fossa [30]. Hypertensive crises (especially renovascular hypertension) have also been reported in women suffering from TA [31]. Overall, the course of the disease is variable, rapid progression of the disease in some patients and late quiescent phase in the others [8].

### 1.4 Diagnosis

Being a systemic disorder, TA affects multiple organs giving a special challenge to the doctors. There is no single diagnostic serologic test available to diagnose TA but non-specific features like fever, fatigue, malaise, arthralgia and night sweats. However, in most of the cases, chest pain has been noted as a common presentation where the doctor does not expect any coronary artery problems otherwise [10,32]. High blood pressure and carotid bruit make it necessary to take blood pressure and examine the peripheral pulses in all the limbs separately. Laboratory investigations are usually non-specific such as raised erythrocyte sedimentation rate (ESR) in 50% cases, increased serum C-reactive protein (CRP) and normocytic normochromic anemia [1,10]. The raised ESR, CRP and anemia reflect underlying inflammatory process. Serum anti-endothelial cell antibodies (AECA) have also been reported in patients with TA by some researchers but their role is still uncertain [33].

Liza Emmans and others [34] reported a case of severe TA affecting left internal carotid artery (LICA), anterior descending artery (LAD) and right coronary artery (RCA) along with occlusion of the left subclavian artery. Angiographic images of stenosed LICA, before Fig 1 and after the stent placement Fig 2 are shown below:
Fig. 1. Angiographic image showing stenosis of left internal carotid artery (LICA) in a patient with TA (Image published with permission from "The Journal of Invasive Cardiology")

Fig. 2. Angiographic image of Left internal carotid artery after the stent placement (Image published with permission from "The Journal of Invasive Cardiology")

Diagnosis is largely based on clinical manifestations and angiographic findings like coarctation, occlusion and aneurysmal dilatations [1,10,35]. Plain x-ray may reveal aortic dilation or mediastinal widening indicating aneurismal dilation of large vessels of the mediastinum. Transthoracic ultrasound examination helps detect dilation of ascending aorta
while transesophageal gives better view of descending aorta. However, angiography is considered to be the gold standard investigation in diagnosing TA [1,36]. Arteriography helps locate the arterial lesion and its appearance. Angiographic techniques are used to perform therapeutic interventions such as angioplasty and stenting of irreversibly stenosed vessels. CT angiography reveals characteristic lesions of aorta and its main branches. Moreno et al. (2005) suggested that positron emission tomography could be helpful in the early diagnosis and follow up of TA [37].

Besides imaging techniques, age less than 40, weak radial pulses, claudication in the extremities, blood pressure differences in the limbs and carotid or subclavian bruits make a clue to the diagnosis of TA. According to American College of Rheumatology Classification Criteria, 3 out of 6 criteria must be fulfilled to make the diagnosis of TA [35], Table-2.

Table 2. Criteria to Diagnose Takayasu’s Arteritis

<table>
<thead>
<tr>
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<th>Criteria</th>
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<tbody>
<tr>
<td>1</td>
<td>Age under 40 at disease onset</td>
</tr>
<tr>
<td>2</td>
<td>Claudication of extremities</td>
</tr>
<tr>
<td>3</td>
<td>Decreased brachial artery pulse</td>
</tr>
<tr>
<td>4</td>
<td>Blood pressure difference more than 10 mmHg between arms</td>
</tr>
<tr>
<td>5</td>
<td>Bruit over subclavian arteries or aorta</td>
</tr>
<tr>
<td>6</td>
<td>Angiogram abnormalities: occlusion or narrowing in aorta or its main branches</td>
</tr>
</tbody>
</table>

1.5 Differential Diagnosis

Certain congenital condition affecting tissue matrix may mimic TA. Marfan and Ehler-Danlos syndromes affect aorta and may mislead the correct diagnosis, however these condition are not associated with stenotic lesion of large vessels that is a common feature of TA [35,38]. TA is also associated with tuberculosis (TB) because of having granulomatous lesion similar to that of TB and trials have benefited both TA and TB with prednisolone and anti-tuberculous therapy [30]. Some autoimmune conditions such as systemic lupus erythematosus (SLE), temporal arteritis, Cogan syndrome and Behçet's disease are associated with large vessel vasculitis and may present with the features like those of TA [39]. However, these conditions have their own specific features differentiating them from TA. Sarcoidosis is also associated with stenotic heart lesions but it can be excluded with the evidence of its characteristic features of skin lesions, hilar adenopathy and Bell's palsy. [35-40]. Moreover, stroke may be one of the complications of TA due to hemodynamic compromise in large arteries [41,42].

1.6 Management

Treatment of TA is based on anti-inflammatory and immunosuppressive therapy along with surgical interventions in severe and stenotic lesions. However, steroid therapy is still the mainstay of managing TA. Most of the cases with TA respond to high-dose oral prednisolone (1-2 mg/kg/day) [1,43]. Steroids suppress the systemic symptoms and hamper the disease progression. When the symptoms and laboratory reports get improved, steroid dose is tapered. The maximum recommended tapering dose of steroids is 10 percent (prednisolone less than 10 mg/day) of the daily dose per week [44]. However, steroid dose can be discontinued or increased depending upon the remissions or exacerbations of the condition respectively.
In glucocorticoid-resistant cases, additional therapy with methotrexate (MTX) or cyclophosphamide is usually added. Studies reveal that steroids followed by MTX are safe and effective in children [45]. European League Against Rheumatism (EULAR) recommends initial high doses of glucocorticoids for the remission of the disease and favors an immunosuppressive agent as an adjunctive therapy [46]. EULAR recommends the starting dose of glucocorticoids 1mg/kg body weight for four weeks and then to taper them off [47]. Retuximab (B-cell depletion therapy) is another option for the patients with TA resistant to glucocorticoids, mycophenolic acid and cyclosporine [48]. Moreover, the combination of steroids and azathioprine has shown promising results in uncontrolled TA [49]. But, the data regarding the use of azathioprine is still lacking and requires more evidence [50]. A study also reveals the efficacy of cyclophosphamide in the management of great vessel vasculitis [51]. However, majority of the cases with refractory TA respond to anti-tumour necrosis factor therapy [52,53]. In short, glucocorticoid resistant cases can be benefited with other immunosuppressive and biological agents. However, Italian Society for Rheumatology does not recommend a biological agent (e.g. anti-TNF-α) as monotherapy due to lack of the evidence. It should be used in combination with glucocorticoids or others. For the same reason, they also contradict the use of biological agents as first line therapy in newly diagnosed patients [54].

Reconstructive vascular surgery should be avoided in active inflammatory phase but cases with critical renovascular hypertension, severe claudication, critical stenosis of cerebral vessels, ischemic crises and moderate aortic regurgitation are indicated to be manipulated surgically [1,55,56]. Ascendo-carotid and thoraco-iliac bypass surgeries have reported be successful in resolving ischemic symptoms related with arterial occlusion [55]. Bear in mind, reconstructive surgery is not widely appreciated until unless no other option is left. However, long term outcome of reconstructive surgery has been reported better in children with low mortality and satisfactory outcome [56].

1.7 Prognosis

TA is a chronic and progressive large vessel vasculitis which follows remitting and relapsing course along with chronic therapy of glucocorticoids. Five year survival has been reported as 88-90% [10]. Comorbidities such as hypertension and complications like aortic regurgitation and aneurysm leads to poor prognosis. Managing the comorbidities and complications promises to increase survival rate. For the last 10 years, the prognosis of TA has been improved, may be due to early diagnosis, use of noninvasive imaging tools and modified medical treatment [57].

2. CONCLUSION

TA is a world-wide but rare and idiopathic chronic inflammatory disease affecting aorta and its main branches. Most of the cases are seen in Asian countries usually presenting with non-specific symptoms of malaise, fever, fatigue or visual problems. American College of Rheumatology Classification Criteria is followed to diagnose TA. However, angiography is the investigation of choice while suspecting an individual suffering from TA. Glucocorticoids (steroids) are the key therapy to treat TA but other agents like MTX or cyclophosphamide are usually added to handle the resistant cases. Affectivity of the treatment is largely based on addressing both the inflammatory and the myointimal proliferative components of the
disease. Surgical treatment is limited to irreversible stenotic lesions as TA mainly involves centrally placed large arteries.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES


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