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Takayasu Arteritis

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Abstract Takayasu arteritis (TA) is an inflammatory disease of the aorta and its primary branches that affects mainly young women. The arterial involvement may cause ischemic manifestations such as limb or abdominal claudication, visual or cerebrovascular symptoms or renovascular hypertention. Anuloaortic regurgitation secondary to aortic root dilatation may also occur. The most important parameters for diagnosis are the young age of onset and the clinical or laboratory evidence of inflammation [fever, carotidynia, elevated erythrocyte sedimentation rate (ESR)] and aortography abnormalities. Carotid and other arteries ultrasound studies showing thickened artery walls may help in the diagnosis, but the main tool for diagnosis has long been the aspect of the digital subtraction arteriography. Nowadays, the arteriography has been replaced by other contrasted enhanced arterial image studies, especially angiotomography or angioresonance. The following criteria are suggestive of the disease: (a) the concomitant presence of stenosis and aneurysm in aorta, (b) presence of stenosis of at least one aortic branch such as subclavian, common carotid, inonimate, vertebral, renal or mesenteric, especially if a few centimeters away from the arterial ostium and (c) association of thickening of the aortic wall with branch stenosis. Two diagnostic criteria sets are commonly used to classify patients as TA: the American College of Rheumatology and the Sharma modified Ishikawa's set.

Keywords Takayasu arteritis · vasculitis · diagnosis criteria · aorta stenosis · aneurysm · aortitis

Takayasu arteritis (TA) is a chronic and progressive inflammatory disease, preferentially occlusive, that involves the aorta and its branches and may also affect the coronary and pulmonary arteries (1). This disease affects young women with a female:male ratio of 9:1. The average age of diagnosis is between 15 and 25 years of age although it has been reported as early as 3 years of age and later in life (2, 3). It has a worldwide distribution, with the greatest prevalence in Asia. In Japan, it has been estimated that 150 new cases occur each year; in contrast, the incidence is 1 to 3 new cases per million people in the United States and Europe. South America countries have been recognized as areas of relatively high incidence (4, 5).

The inflammatory process that occurs in this vasculitis may be localized to a portion of thoracic or abdominal aorta and branches, or may involve the entire extension of these vessels. Although there is considerable variability in disease expression (6), the initial vascular lesion frequently occurs in the left middle or proximal subclavian artery. As the disease progresses, the left common carotid, vertebral, brachiocephalic, right middle or proximal subclavian artery, right carotid and vertebral arteries, and aorta may also be affected.

Pathogenesis

The cause of TA remains unknown. The geographic clustering suggests that genetic and environmental factors may play an important role. Cellular and humoral immune mechanisms have been implicated in the pathogenesis of TA. The histologic findings are particularly supportive of a cell-mediated process. In this regard, natural killer cells, cytotoxic T cells and γδ T lymphocytes have been demonstrated in aortic tissue from TA patients. These cells may cause vascular injury by releasing large amounts of cytolytic compound named perforin. Moreover, expression of heat shock protein-65 might facilitate recognition and

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adhesion of the infiltrating cells (7). Increased expression of intracellular adhesion molecule 1 (ICAM-1) and human leukocyte antigen (HLA) class I and II antigen in the vessel wall also supports the concept of cell-mediated process.

A role for humoral immune mechanisms is suggested by the presence of hypergammaglobulinemia, rheumatoid factor and antiendothelial antibodies.

Clinical Features

Patients with TA present the following symptoms on physical examination: bruits, diminished or absent pulses and asymmetric blood pressure measurements between extremities. Because the subclavian arteries are a frequent site of vessel stenosis, blood pressure measurement in one or both arms may not be representative of aortic root pressure.

Hypertension has been reported to occur in 35–77% of TA patients (8, 9, 10, 11, 12, 13, 14). It is an important cause of morbidity in TA patients and contributes to renal, cardiac and cerebral injuries. In India, TA is the most common cause of renovascular hypertension, accounting for over 60% of all cases.

At the time of diagnosis, approximately 20% of patients with TA are clinically asymptomatic, with the disease being detected solely by abnormal vascular findings on examination. The remaining 80% of patients with TA present a variety of signs and symptoms that can be subdivided into two groups: those caused by vascular injury and those caused by systemic inflammation. The constitutional or musculoskeletal symptoms are observed in 20–40% of the patients and may dominate the presentation in approximately one-third of all cases. They are characterized by fatigue, malaise, weight loss, night sweats, fever, artralgias or myalgias.

Vascular symptoms are a direct result of current or previous arteritis. Active inflammation may cause tenderness over vessels and carotidynia, which is observed in 2–32% of patients. Vessel inflammation typically results in either stenosis or aneurysm formation. Arterial stenosis may present with signs or symptoms of diminished blood flow to regions supplied by the affected vessel, and aneurysms can rupture or cause valvular incompetence when involving the aortic root. The frequencies of common symptoms and signs are listed in Table 15.1 (8, 9, 10, 11, 12, 13, 14).

Stenosis or occlusion of vessels that supply central nervous system (vertebral and carotid arteries) may diminish perfusion and cause injury to the brain manifested by transient ischemic attacks, stroke, dizziness, syncope, headache or visual changes.

Visual symptoms chiefly result from retinal ischemia produced by narrowing/occlusion of the internal carotid circulation or as a direct complication of hypertension.

Cardiac manifestations are frequently related to aortic valvular regurgitation from dilation of the aortic root. Up to 25% of patients may also develop coronary vessel stenosis. The patients with cardiac involvement may present with dyspnea, palpitations, angina, myocardial infarction, heart failure or sudden death.

The pulmonary arteries are involved in up to 50% of cases; however, symptoms related to pulmonary arteritis are less common. Pulmonary manifestations due to pulmonary vasculitis are less common and include chest pain, dyspnea and hemoptysis. Anatomopathological studies have reported a frequency as high as 50% of pulmonary arteries involvement.

Table 15.1. Common symptoms and signs in Takayasu arteritis.

	Brazil (n = 73)	China (n = 530)	India (n = 106)	Japan (n = 52)	Korea (n = 129)	Mexico (n = 107)	USA (n = 60)
Fatigue (%)	–	–	–	27	34	78	43
Weight loss (%)	27.5	–	9	–	11	22	20
Musculoskeletal (%)	26	–	5	6	–	53	53
Claudication (%)	57	25	–	13	21	29	90
Headache (%)	45	–	44	31	60	57	42
Visual changes (%)	–	10	12	6	20	8	30
Syncope dizziness (%)	29	14	26	40	36	13	35
Palpitations (%)	–	–	19	23	23	43	10
Dyspnea (%)	–	11	26	21	42	72	–
Carotidynia (%)	–	–	–	21	2	–	32
Hypertension (%)	35.5	60	77	33	40	72	35
Bruit (%)	64.5	58	35	–	37	94	80
Decreased pulses (%)	85	37	–	62	55	96	60
Asymmetric blood pressure (%)	–	–	–	–	–	–	47

The most common skin lesions observed includes erythema nodosum or pyoderma gangrenosum over the legs. The lesions frequently show vasculitis of small vessels on biopsy.

Laboratorial Findings

There is no laboratory study that is diagnostic for TA, but the disease is usually associated with nonspecific findings of inflammation. In fact, acute-phase reactants such as an elevated erythrocyte sedimentation rate (ESR), increased serum C-reactive protein and alpha-2 globulin concentrations, and hypoalbuminemia are a reflection of underlying inflammatory process. These tests are not always precise or invariably reliable indicators, but usually reflect the disease activity.

Imaging Findings

Imaging of the aorta and major arteries is usually necessary to confirm the diagnosis of TA.

Arteriography: The most frequent arteriographic finding is stenosis, which occurs in 85% of patients. Vessel occlusion or irregularity is also commonly seen (Figures 15.1 and 15.2). Aneurysms may be saccular or fusiform and typically affect the aorta rather than its branches. Varying patterns of vessel involvement have been observed in different populations with lesions of the ascending aorta and aortic arch being more common in Japanese patients, whereas involvement of the abdominal aorta and renal arteries is more typical in patients from India and Brazil (8, 15, 16). Arteriography may define the localization and appearance of the arterial lesion and may also allow a therapeutic intervention (balloon dilatation and/or stent) to follow the same puncture.

Although arteriography frequently provides clear outlines of the lumen of involved arteries, it does not allow arterial wall thickening to be assessed and is an invasive test associated some risks such as an important exposure to contrast and radiation. Therefore, if a therapeutic intervention is not anticipated, a less invasive imaging technique may be preferred.

Computed tomography (CT) or magnetic resonance imaging (MRI) scans allow visualization of both vascular lumen and arterial wall thickness, improving the accuracy of TA diagnostic. It has been demonstrated that T2-weighted MRI, sensitive to liquid content, can detect arterial wall edema. Moreover, T1-weighted MRI after gadolinium injection permits visualization of the aortic wall enhancement, which could reflect inflammatory and/or fibrosis vascular lesions in TA patients. MRI improves the mapping of arterial lumen, as well as detecting aortic wall thickness disease. The degree of wall thickness and the presence of edema and/or delayed enhancement in the aortic wall could provide data regarding the diagnosis, control and follow-up of TA patients (17, 18, 19).

Diagnostic Criteria

(a) American College of Rheumatology 1990 criteria for the classification of TA (5).

FIGURE 15.1. Arteriography. Left panel: arterial phase shows occlusion of right subclavian artery. Right panel: venosus phase shows retrograde blood flow by vertebral artery characterizing subclavian steal syndrome.

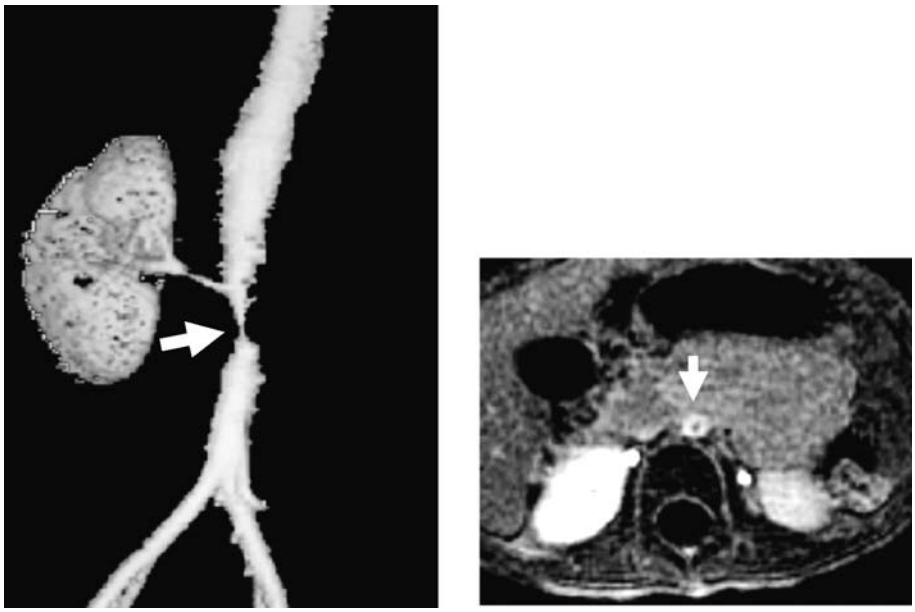

FIGURE 15.2. Left panel: magnetic resonance imaging (MRI) shaded-surface reconstruction showed aortic stenosis at the renal level (arrow) and occlusion of the left renal artery. Right panel: axial delayed enhancement in the abdominal aorta wall at the infra renal level associated with stenosis (arrow).

Criterion	Definition
Age at disease onset ≤40 years	Development of symptoms or findings related to TA at age ≤40 years
Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of one or more extremities, while in use, especially the upper extremities
Decreased brachial artery pressure	Decrease pulsation of one or both brachial arteries
Blood pressure difference >10 mmHg	Difference of >10 mmHg 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	Arteriografic narrowing or occlusion of the entire aorta, its primary branches or larger arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia or similar causes; changes usually foci or segmental

For purposes of classification, a patient shall be said to have TA if at least three of these six criteria are present. The presence of any three or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%.

(b) Sharma's criteria for TA (Ishikawa's criteria modified according to Sharma et al.) (20, 21).

Three major criteria:

1. Left mid-subclavian artery lesion: the most severe stenosis or occlusion present in the mid portion from the point 1 cm proximal to the vertebral artery orifice up to that 3 cm distal to the orifice determined by angiography.
2. 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 orifice determined by angiography.
3. Characteristic signs and symptoms of at least 1 month duration: These include limb claudication, pulselessness or pulse differences in limbs, an unobtainable or significant blood pressure difference (>10 mmHg systolic blood pressure difference in limb), fever, neck pain, transient amaurosis, blurred vision, syncope, dyspnea or palpitations.

Ten minor criteria:

1. High ESR: unexplained persistent high ESR >20 mm/h (Westergren) at diagnosis or presence of the evidence in patients history.
2. Carotid artery tenderness: unilateral or bilateral tenderness of common arteries on palpation. Neck muscle tenderness is unacceptable.
3. Hypertension: persistent blood pressure >140/90 mmHg brachial or >160/90 mmHg popliteal.
4. Aortic regurgitation or Anuloaortic ectasia: aortic regurgitation by auscultation or Doppler echocardiography or angiography; or Anuloaortic ectasia by angiography or two-dimensional echocardiography.
5. Pulmonary artery lesion: 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.

6. Left mid common carotid lesion: presence of the most severe stenosis or occlusion in the mid portion of 5 cm in length from the point 2 cm distal to its orifice determined by angiography.
7. Distal brachiocephalic trunk lesion: presence of the most stenosis or occlusion in the distal third determined by angiography.
8. Descending thoracic aorta lesion: narrowing, dilatation or aneurysm, luminal irregularity or any combination determined by angiography: tortuosity alone is unacceptable.
9. Abdominal aorta lesion: narrowing, dilatation or aneurysm, luminal irregularity or aneurysm combination.
10. Coronary artery lesion: documented on angiography below the age of 30 years in the absence of risk factors like hyperlipidemia or diabetes mellitus.

Presence of two major or one major and two minor criteria or four minor criteria suggests a high probability of TA.

Criticism on the Diagnosis Criteria

1. The diagnostic imaging criteria of TA are based on vascular lesions detected by conventional angiographer (CA), which represents a lumen analysis method. CA does not characterize the thickness in aortic wall; it is a limitation of this method. Alterations of aortic wall are frequently observed in TA patients, mainly in earliest period of this disease. Conversely, MRI or CT imaging scan allows visualization of both vascular lumen and arterial wall thickness, improving the accuracy of TA diagnostic.
2. In case of patients with exclusive involvement of abdominal aorta or its branches, it is not possible to fulfill Sharma's criteria. These criteria consider subclavian arteritis as the main involvement in TA diagnosis. On the contrary, the incidence of lesions in aortic branches varies depending on the geographical region analyzed, and the involvement of abdominal aorta and its branches is more frequently observed in countries as Brazil and India. Consequently, sensitivity will be decreased in these populations.

Treatment

Therapeutic approach are often guided by individual patient variables that include disease activity, the location and severity of lesions, availability of collateral circulation, nature and intensity of symptoms, and the risk of drug toxicity.

The basis of therapy for TA is glucocorticoids (GCs). The GC dose can be gradually reduced when the symptoms and laboratory inflammatory markers have improved. For patients with disease refractory to GCs, immunosuppressive agents are recommended such as methotrexate, azathioprine, mycophenolate mofetil and cyclophosphamide. Anti-tumor necrosis factor agents are also other therapeutic options in severe and unresponsive cases.

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