Takayasu’s arteritis: clinical and therapeutic aspects in 36 patients

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ORIGINAL ARTICLE

ABSTRACT

Background: Takayasu arteritis is a chronic vasculitis often with delayed diagnosis due to the nonspecific presentation of clinical symptoms in its initial phase. Treatment includes immunosuppression drugs. Surgical treatment, when necessary, should be avoided in the acute phase.

Objective: To describe clinical, laboratory and vascular findings in Takayasu’s arteritis from 1977 through 2006.

Methods: The sample was comprised of 36 patients (10 Caucasians, 35 women), mean age of 31.7 (±13.7) years, and significant prevalence in the forth decade (p < 0.005). Disease course was 3 years and time until diagnosis was 7.9 years. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were used to assess disease activity, and duplex scan to measure carotid artery intima-media wall thickness.

Results: Hypertension was present in 85.2%, and upper and lower limb claudication in 69.5 and 30.5%, respectively. ESR was > 60 mm in 50% of the sample (p < 0.005). CRP mg/dL was performed in 18 cases, ranging from 0.4-25 on admission to 0.11-1.9 during disease course. Autoimmune diseases, tuberculosis and HIV correlated in 19.4, 8.3 and 2.7%, respectively. Major aortic lesions were detected in 22.2% (four occlusions, two infrarenal aneurysms, one thoracic aneurysm). Other arteries involved renal, subclavian and one carotid occlusion (19%), and some level of lower limb occlusion (25%). Intima-media thickness was stratified in ≥ 3 mm (41.6%), < 3 and ≥ 1.7 (19.4%), < 1.7 and ≥ 1.2 (8.37%), and < 1.2 mm (30.50%) (p < 0.005). Glucocorticoids were used in 61%, azathioprine in 16.6%, and azathioprine combined with cyclophosphamide in 8.3%. Surgical and endovascular procedures were performed in 30.5%. Two
patients died due to cardiovascular diseases.

Conclusions: Carotid intima-media thickness, CRP, and ESR are important markers for the follow-up of Takayasu’s arteritis. Delay in diagnosis is an important issue for Takayasu’s progression, since it may reduce morbidity and mortality rates.

Keywords: Takayasu’s arteritis, imaging diagnosis, duplex scan imaging, carotid, aorta, intimal thickening clinical treatment, surgical treatment.

RESUMO

Contexto: A arterite de Takayasu é uma vasculite crônica, geralmente com diagnóstico tardio devido à pouca especificidade dos sintomas durante a fase inicial do acometimento vascular. A terapêutica de eleição é o uso de imunossupressores. O procedimento cirúrgico, quando necessário, é sempre evitado na fase aguda.

Objetivo: Descrever alterações clínicas, laboratoriais e vasculares de arterite de Takayasu no período de 1977 a 2006.

Método: A amostra compreendeu 36 pacientes – 10 brancos, 35 mulheres, idade média de 31,7 anos (±13,7), com prevalência significante na quarta década (p < 0,005). Evolução de 3 anos e período até o diagnóstico de 7,9 anos. Velocidade de hemossedimentação (VHS) e proteína C reativa (PCR) avaliaram atividade da doença, e o duplex scan aferiu a espessura médio-intimal da artéria carótida.

Resultados: Hipertensão arterial sistêmica e claudicação de membros superiores e inferiores foram ressaltados em 85,2, 69,5 e 30,5%, respectivamente. O resultado da VHS foi > 60 mm em 50% da amostra (p < 0,005). PCR mg/dL foi realizado em 18, variando de 0,4-25 na admissão para 0,11-1,9 na evolução. Doença auto-imune, tuberculose e HIV correlacionaram-se em 19,4, 8,3 e 2,7%, respectivamente. Lesões aórticas foram significativas em 22% (quatro oclusões, dois aneurismas infra-renais, um torácico). Em 19,4%, foram acometidas artérias renais e subclávias uma oclusão bilateral de carótidas, e em 25% os membros inferiores. A espessura médio-intimal da carótida comum foi estratificada em: ≥ 3 mm, < 3 e ≥ 1,7, < 1,7 e ≥ 1,2 e < 1,2 mm, representando 41,6, 19,4, 8,37 e 30,50%, respectivamente (p < 0,005). Glicocorticóides foram utilizados em 61,1%, azatioprina em 16,6%, e associada a ciclofosfamida em 8,3%. Procedimento cirúrgico ou endovascular foi realizado em 30,5% com dois óbitos por complicações cardiovasculares.

Conclusões: A VHS, PCR, e a espressura médio-intimal nas carótidas são importantes marcadores de acompanhamento da arterite de Takayasu. O período entre os sintomas e o diagnóstico deve ser abreviado, com redução da morbimortalidade.

Palavras-chave: Arterite de Takayasu, diagnóstico por imagem, imagem por duplex scan, carótida, aorta, espessamento intimal, tratamento clínico, tratamento cirúrgico.

Introduction

Takayasu’s arteritis (TA) is a chronic progressive inflammatory disease characterized as chronic granulomatous vasculitis, which involves the aorta and its main branches.1-6 There is transmural granulomatous inflammation, which may cause stenosis, occlusion, dilatation and/or formation of aneurysms in affected arteries. Its diagnosis remains a great challenge due to unspecific clinical and laboratory evidence.1-7
Diagnostic criteria based on changes in arterial wall, by determining the degree of wall thickening, can be assessed and followed by duplex scan, angiography, computed tomography (CT) and magnetic resonance angiography (MRA). Recent studies have shown that MRA, TC and angiography are very specific for detailing lesions in the aortic wall and its branches. Follow-up using duplex scan can be used in the assessment of the common carotid medial-intimal complex thickness, correlating it with TA course and clinical and laboratory aspects.

Several diseases have TA as differential diagnosis, such as Marfan’s syndrome, Ehlers-Danlos, fibromuscular dysplasia, among other vasculitis. It has higher incidence in Japan, China, India and Mexico. Reported incidence is 1.2, 2.6 and 2.9/million/year in the USA, Europe and Mexico respectively. Incidence in Asia is 100 times higher. In 1990, it was included in the list of hard-to-treat diseases by the Japanese government, and until 2002, 5,000 patients had been recorded. It should be stressed that TA has a 90% incidence in women aged 18-40 years.

Etiology, etiopathogenesis and clinical manifestations

The etiologic mechanism of TA remains unknown. Chauhan et al. reported that auto-antibodies (AAECA) work against the heat-shock protein with increase in E-selectin expression and vascular cell adhesion 1, as well as increase in production of IL-4, IL-6 and IL-8. They reported induction of apoptosis in the aortic endothelium, suggesting that AAECA may cause vascular dysfunction.

Verma et al. reported significantly higher IL-12 serum levels in TA. Tripathy et al. investigated cytosine levels T-lymphocyte cells (T cells), reporting increased percentages of tumor necrosis factor (TNF-) and reduced IL-2 percentages, produces by T cells in the acute stage of TA. Numano & Kobayashi showed incidence of carriers of HLA B52 antigen in the Japanese population, with higher risk for development of TA.

TA is inserted in the group of systemic primary vasculitis, characterized by inflammation and fibrinoid necrosis. Clinical assessment is variable, depending on location and extension of affected vessels, inflammatory process and triggered systemic effects, with disease course in three stages.

The first stage is focused on the inflammatory period, with presence of pulses and unspecific symptoms, such as fever, arthralgia, myalgia, night sweating, anorexia, headache, dizziness, malaise, erythema nodosum, asthenia, and weight loss. At this moment there is a migration of inflammatory cells through the vasa vasorum until the arterial medial layer.

The second stage exacerbates vascular inflammation, with pain in the course of the vessel (carotidynia). The inflammatory process becomes intense and concentrated on the medial layer, with destruction of collagen fibers and cell migration into the adventitia, and the endothelial lesion starts the process of stenosis, occlusion and dilatation.

The last stage is fibrotic, with stenosis, occlusion or aneurysmal dilatation. There are ischemic changes secondary to arterial occlusions, more frequent changes in peripheral arterial pulses (absence, reduction in amplitude or 30 mmHg difference in blood pressure in relation to the heterologous limb), murmur and thrill in arterial courses, sensitive carotid arteries, paresthesias and claudication, especially in the upper limbs (UL).

Hypertension due to renal artery stenosis in TA is the most common cause of secondary hypertension reported in Asia. There is also mitral or aortic regurgitation, dilated cardiomyopathy...
due to diffuse vascular involvement of the myocardium, neurological (syncope, headache, stroke), ophthalmologic (retinopathy due to hypoperfusion), formation of arteriovenous shunt, renal failure, and dermatological involvement, \textsuperscript{26} erythema nodosum, pyoderma gangrenosum and Raynaud's phenomenon.\textsuperscript{6,27,28}

At the Angiology Outpatient Clinic of Faculdade de Ciências Médicas (FCM), at Hospital Universitário Pedro Ernesto (HUPE), Universidade do Estado do Rio de Janeiro (UERJ), the classification criteria of the American College of Rheumatology (ACR) for TA (Table 1) and the definition of TA proposed by the Chapel Hill Consensus Conference\textsuperscript{29} are used as auxiliary methods in diagnosis. The activity parameters proposed by the National Institute of Health (NIH) are routinely applied to measure disease activity. Failure in therapeutic intervention is considered when there are persistent clinical symptoms of activity, recurrence in therapeutic reduction or unacceptable toxicity, presence of new lesions or even evolution of the angiologic type assessed by duplex scan and/or arteriographic type.\textsuperscript{30}

Table 1 - Diagnostic criteria of the ACR with 90.5% sensitivity and 97.8% specificity

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 40 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in brachial pulses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limb claudication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mmHg difference in systolic BP of UL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murmurs in subclavian and aortic arteries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiographic changes in the aorta and its main arches</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BP = blood pressure; UP = upper limbs. Adapted from Hunder et al.\textsuperscript{38}

The classification of lesions using angiography revised in the International TA Conference,\textsuperscript{29} in 1994, and published by Hata\textsuperscript{31} divides the disease into subtypes: type 1, which affects aortic arch branches; type 2a, ascending aorta, aortic arch and its branches; type 2b, similar to type 2a, including thoracic aorta; type 3, thoracic aorta, abdominal aorta and/or renal arteries; type 4, abdominal aorta and/or renal arteries; type 5, combination of types 2b and 4.\textsuperscript{16,29,31}

As to type of vascular lesion, stenotic and occlusive lesions are predominant, followed by aneurysmal dilatations.\textsuperscript{24} Of these, aneurysms have variable incidence, higher in Southeast Asia and lower in the American continent.\textsuperscript{24}

This study aimed at: 1) describing clinical, laboratory and vascular changes assessed in 36 patients followed from 1977 through 2006; and 2) describing the changes in carotid wall using duplex scan.

**Method**

Thirty-six patients were followed at the Angiology Unit at HUPE, UERJ, from 1977 through 2006. Demographic data, such as race, gender and age, and clinical data, such as claudication in the UL and lower limb (LL), hypertension, autoimmune disease, tuberculosis and human immunodeficiency virus (HIV), time of diagnosis and disease period in years, were collected.

Erythrocyte sedimentation rate (ESR) mm/dL and C-reactive protein (CRP) mg/dL were used as markers. The duplex scan was used to assess carotid, renal, subclavian and aortic arteries. Wall thickness of the carotid arteries was stratified into four categories: ≥ 3 mm; < 3 and ≥ 1.7 mm; <
1.7 and ≥ 1.2 mm; and < 1.2 mm, used to evaluate disease course.

Glucocorticoids and immunosuppressants, such as azathioprine (AZO), methotrexate and cyclophosphamide, were used alone or combined. Surgical and/or endovascular treatments were performed (bypasses, angioplasties with or without stenting or endografting).

The database was typed and analyzed using the Epi-Info and Statistical Package for the Social Sciences (SPSS). The chi-square test analyzed the variables, with significance of p < 0.05.

This study was approved by the Research Ethics Committee of FCM, HUPE, UERJ on February 28, 2008.

Results

The sample was comprised of 36 patients – 10 Caucasians, 35 women, mean age of 31.7±13.7, with significant prevalence in the fourth decade (p < 0.005). Hypertension was present in 85.2%, and LL and UL claudication in 30.5 and 69.5%, respectively.

Autoimmune diseases, pulmonary and extrapulmonary tuberculosis and HIV were correlated with TA in this cohort in 19.4, 8.3 and 2.7%, respectively.

Time between symptom onset and diagnosis was 7.9 years, with disease progression of 3 years in 55% of cases and 10 years in 75%, until diagnosis.

ESR was considered as a marker of acute stage, with 50% > 60 mm, and the others were between 26 and 28 mm (p < 0.005) (Table 2). CRP mg/dL was performed in 18, ranging from 0.4-25 on admittance to 0.11-1.9 during disease course.

<table>
<thead>
<tr>
<th>Clinical and laboratory variables and time of disease from symptom onset to diagnosis</th>
<th>n</th>
<th>%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>31</td>
<td>86.1</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Lower limb claudication</td>
<td>11</td>
<td>30.5</td>
<td></td>
</tr>
<tr>
<td>Upper limb claudication</td>
<td>25</td>
<td>69.5</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>7</td>
<td>19.4</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>3</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>1</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Time between symptom onset and diagnosis (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.9</td>
<td>36</td>
<td>100</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>55</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>10</td>
<td>27</td>
<td>75</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>ESR (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 60</td>
<td>18</td>
<td>50</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>&gt; 26</td>
<td>31</td>
<td>86.1</td>
<td></td>
</tr>
</tbody>
</table>

ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus.
The duplex scan was performed in 88% for assessment of carotid, subclavian, vertebral and aortic arteries.

Aortic lesions were detected in eight (22%) patients: four occlusions, two infrarenal aneurysms and a thoracic aneurysm. Other affected arteries were the renal and subclavian (19%), one bilateral occlusion of carotid arteries and some degree of stenosis in the LL (25%). Duplex scan showed that the carotid arteries were the most affected (47.2%).

Arterial wall thickness was performed in 83% in the common carotid artery, with the following values: ≥ 3 mm, < 3 and ≥ 1.7 mm, < 1.7 and ≥ 1.2 mm, and < 1.2 mm in 42.8, 18, 7.1 and 32%, respectively (p < 0.005) (Table 3). Figures 1, 2 and 3 illustrate vascular changes. Duplex scan with carotid artery intimal thickening, before and after immunosuppressive treatment, showing reduction in medial-intimal thickening from 1.8 to 0.9 mm; arteriography with supraaortic stenosis; and MRA with abdominal aortic stenosis, respectively.

Table 3 - Affected arteries shown by duplex scan and variation in parietal thickening (mm) of the carotid artery

<table>
<thead>
<tr>
<th>Arterial involvement: pariatal thickening (nm)</th>
<th>n</th>
<th>%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid artery</td>
<td>17</td>
<td>47,2</td>
<td></td>
</tr>
<tr>
<td>&gt; 3</td>
<td>14</td>
<td>41,1</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>1,71-3</td>
<td>6</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>1,21-1,7</td>
<td>3</td>
<td>8,8</td>
<td></td>
</tr>
<tr>
<td>&lt; 1,21</td>
<td>11</td>
<td>32,1</td>
<td></td>
</tr>
<tr>
<td>Aorta</td>
<td>7</td>
<td>19,4</td>
<td></td>
</tr>
<tr>
<td>Subclavian artery</td>
<td>5</td>
<td>13,8</td>
<td></td>
</tr>
<tr>
<td>Renal artery</td>
<td>3</td>
<td>8,3</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 - A) Duplex scan to assess common carotid artery intimal thickening (1.8 mm); B) after treatment (0.9 mm)
Glucocorticoids were used in 61%, AZO in 16.6% and AZO combined with cyclophosphamide in 8.3%.

Surgical or endovascular procedure was performed in 30.5%: 16% "bypasses" and angioplasties, 5% stenting and 2% endografting, with two deaths due to cardiovascular complications.

**Discussion**
Incidence in young women until the fourth decade is consensual in the literature, confirmed by a Chinese study of 530 patients, in which 395 (74.5%) patients were women. In our population, such percentage was higher, i.e., of the 36 patients, 97.2% were female.

It is agreed that genetic elements, infectious agents and autoimmune factors are related to TA course, highlighting the possibility of *Mycobacterium tuberculosis* (MT), and arguable luetic. In this population, the correlation between infectious agents occurred in 11.1%, with no statistical significance.

Relationship between TA and MT is reported as granulomatous lesion, cutaneous reactivity to its purified protein derivative (PPD), variable frequency with active tuberculosis and histological aspect of lymphadenopathy, suggesting mycobacterial infection, although the bacilli were not found in tissue lesions. In the present study, 8.3% had reactivity to PPD; two were associated with lymphadenopathy and one was related to the erythema nodosum. They were submitted to biopsy, confirming MT, and one was in chemoprophylaxis. Two facts need to be evaluated: the possibility of undetected infection and autoimmune reactions by the mycobacterium in TA.

Clinical manifestations are variable and dependent on intensity, site and velocity of the pathological process. Vascular lesions and hypertension develop in more than 50%, and may be considered essential, even in the absence of significant lesions. According to Sheikhzadeh et al., hypertension was reported in 50-75%, as a consequence of renal and aortic artery complacence. In our population, 31 (86.1%) had hypertension, possibly due to involvement of renal arteries.

Diagnosis based on clinical course and laboratory tests, more specifically serum markers of disease activity, are useful. ESR and ultrasensitive CRP, despite being unspecific, are the most widely used. According to Salvarani et al., normal ESR results do not discard the hypothesis of an active disease stage, and is used for TA course and therapeutics.

Ultrasensitive CRP and interleukin-6 have proven to be more specific for TA. Biopsies associated with ESR showed that 40% had incorrect diagnoses of disease stage, since some reported as in remission were still active.

In our study, ESR used as a marker of disease activity was statistically significant.

Imaging diagnosis has more effective results. Arteriography was considered the gold standard for diagnosis. Being invasive helps to bring accurate information about wall lesion and arterial lumen. The duplex scan is specific to assess disease activity. Finally, MRA is currently very specific to assess degree of aortic stenosis.

Assessment using duplex scan in the initial stage of TA, when there are unspecific symptoms, proved to be effective, pointing out parietal changes without causing hemodynamic repercussion with indication and early start of therapeutics, controlling TA progress.

Park et al. classified carotid medial-intimal thickening by comparing activity (2.5-5 mm) and inactivity (1.1-2 mm): they indicate vessel diameter ≥ 10 mm in activity and ≤ 0.7 mm as inactive stage. Andrews & Mason, in agreement with these parameters, excluded non-homogenous and calcified atherosclerotic plaques in the vessel wall. In this study, such parietal changes were more evident, with varied degrees of hemodynamic changes.

Serial duplex scan did not show correlation with improvement brought by the treatment, suggesting further studies.

In this population, duplex scan was used in 34 (94.4%) patients, with annual follow-up, stressing
that increase in arterial wall thickening was significant.

TA therapy is based on corticotherapy. Whenever necessary, other immunosuppressants are associated, such as methotrexate, AZO, cyclophosphamide, mycophenolate mofetil and anti-TNF.\textsuperscript{17,42,45-49}

Maksimowicz-McKinnon et al.,\textsuperscript{48} in a prospective study, reported that 73% patients required association with corticoid at doses lower than 10 mg in the following order: methotrexate, AZO, mycophenolate mofetil, cyclophosphamide and infliximab (anti-TNF).

Drugs such as infliximab need wider studies to assess their efficacy; to date, its results are satisfactory.\textsuperscript{44-48}

Hunder\textsuperscript{30} and Jennete et al.,\textsuperscript{29} at the International Consensus Conference and in the NIH study, respectively, stressed satisfactory remission results with corticotherapy in association with methotrexate in up to 60%. Few patients did not achieve remission and required anti-TNF.\textsuperscript{46} In our study, 22 (61.1%) used corticotherapy in regressive doses, and the others used other immunosuppressants in association to maintain remission.

A retrospective study\textsuperscript{15} reported 513 cases of resection of the ascending aorta due to aneurysms; of these, only 33 had anatomopathological diagnosis of vasculitic aneurysms. Isolated renal artery aneurysm is rare.\textsuperscript{49}

In our study, we point out the stenotic lesions, followed by occlusive lesions and aneurysms (two infrarenal and one pulmonary), in addition to a left subclavian aneurysm associated with the ascending aortic aneurysm. As corroborated by other studies,\textsuperscript{50,51} the lesions are mostly stenotic or occlusive.

Some patients do not achieve remission even with proper treatment, resulting in progressive vascular injury, with indication of surgical procedure. The results of conventional surgery had longer graft patency time. The endovascular procedure has better results with angioplasties and without stenting. Nowadays, immunosuppressant-covered pharmacological stent is under assessment.\textsuperscript{46}

Surgical procedures were performed in 11 patients (30.5%) of this study, such as conventional bypasses, followed by angioplasties. Use of angioplasty and stent should be stressed, which occluded 4 months later and required intervention. The retrospective study by Sato et al.,\textsuperscript{44} in our country, including 30 patients, corroborates indication of surgical procedure in 30%, despite clinical treatment.\textsuperscript{44}

In our population, there were two (5.5%) deaths due to disease-related vascular complications.

**Conclusions**

ESR, CRP and assessment of arterial wall thickness using duplex scan were important markers for disease follow-up. The observation of clinical routines is necessary for disease diagnosis at the shortest time as possible, reducing morbidity and mortality rates. Surgical procedures, when performed in the stage of TA activity, showed negative results; however, in the inactive stage or in remission, results were satisfactory.
References


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