REVISTA BRASILEIRA DE REUMATOLOGIA

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Original article

Brazilian multicenter study of 71 patients with juvenile-onset Takayasu's arteritis: clinical and angiographic features☆

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ARTICLE INFO

Article history:
Received 5 December 2014
Accepted 5 September 2015
Available online 18 February 2016

Keywords:
Takayasu's arteritis
Child
Teenager
Image

ABSTRACT

Objective: To describe the clinical and angiographic characteristics of Takayasu's arteritis in Brazilian children and adolescents.
Methods: A retrospective data collection was performed in 71 children and adolescents followed in 10 Brazilian reference centers in Pediatric Rheumatology. The evaluation was carried out in three different time points: from onset of symptoms to diagnosis, from the 6th to 12th month of diagnosis, and in the last visit.
Results: Of 71 selected patients, 51 (71.8%) were girls. The mean age of onset of symptoms and of time to diagnosis was 9.2 (±4.2) years and 1.2 (±1.4) years, respectively. At the end of the study, 20 patients were in a state of disease activity, 39 in remission and 5 had evolved to death. The most common symptoms in baseline assessment, second evaluation, and final evaluation were, respectively: constitutional, musculoskeletal, and neurological symptoms.

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http://dx.doi.org/10.1016/j.rbre.2016.01.004

A decrease in peripheral pulses was the most frequent cardiovascular signal, and an increase in erythrocyte sedimentation rate was the most frequent laboratory finding in all three evaluation periods. The tuberculin test was positive in 41% of those tested. Stenosis was the most frequent angiographic lesion, abdominal artery was the most affected segment, and angiographic type IV the most frequent. Most (90%) participants were treated with glucocorticoids, 85.9% required another immunosuppressive drug, and 29.6% underwent angioplasty.

Conclusion: This is the largest study on juvenile-onset Takayasu arteritis, and a high number of patients under the age of 10 years, with predominance of constitutional symptoms early in the disease, was observed.

Estudo multicêntrico brasileiro de 71 pacientes com arterite de Takayasu juvenil: características clínicas e angiográficas

Palavras-chave:
Arterite de Takayasu
Criança
Adolescente
Imagem

RESUMO

Objetivo: Descrever as características clínicas e angiográficas da arterite de Takayasu em crianças e adolescentes brasileiros.

Métodos: Foi realizada coleta retrospectiva de dados de 71 crianças e adolescentes acompanhados em 10 centros brasileiros de referência em reumatologia pediátrica. A avaliação foi feita em 3 tempos diferentes: início dos sintomas até o diagnóstico, do 6° ao 12° mês de diagnóstico e última consulta.

Resultados: Dos 71 pacientes selecionados, 51 (71,8%) eram meninas. As médias de idade de início dos sintomas e de tempo até diagnóstico foram 9,2 anos (±4,2) e 1,2 anos (±1,4), respectivamente. No final do estudo, 20 pacientes estavam em atividade de doença, 39 em remissão e 5 haviam evoluído ao óbito. Os sintomas mais frequentes nas avaliação inicial, segunda avaliação e avaliação final foram, respectivamente: os constitucionais, os musculoesqueléticos e os neurológicos. A redução de pulsos periféricos foi o sinal cardiovascular mais frequente e a elevação da velocidade de hemossedimentação foi o achado laboratorial mais frequente nos três períodos de avaliação. O teste tuberculínico foi reagente em 41% daqueles que o realizaram. A estenose foi a lesão angiográfica mais encontrada, a artéria abdominal foi o segmento mais afetado e tipo angiográfico IV o mais frequente. A maioria (90%) fez terapia com glicocorticoides, 85,9% necessitou de outro imunossupressor e 29,6% foi submetido à angioplastia.

Conclusão: Este é o maior estudo de arterite de Takayasu juvenil e nós pudemos observar elevado número de pacientes com idade inferior a 10 anos e a predominância de sintomas constitucionais no início da doença.

Introduction

Takayasu's arteritis (TA) is a chronic vasculitis that affects large- and medium-caliber arteries and is accompanied by high morbidity, due to an impaired blood supply to organs and limbs. The disease is rare and affects predominantly young female adults, being most prevalent in East Asian countries. This makes TA a poorly characterized disease in the pediatric population, particularly in Western countries. The descriptions of the disease in the pediatric population, including infants, has increased in recent decades, often reaching 32% of patients aged under 20 years.[1–5]

Clinical signs and symptoms found in patients with juvenile-onset TA are similar to those found in adults, for instance, the presence of constitutional, neurological and musculoskeletal symptoms, high blood pressure, a decrease of peripheral pulses and presence of vascular murmur. However, the initial clinical manifestations seem to be more insidious and nonspecific in children.[4,6–9] This may contribute to the greater delay of diagnosis in the pediatric age group, which is up to four times higher than that for adults.[2]

The world literature on juvenile-onset AT are scarce, being derived from specific populations with small numbers of patients.[3–9] The aim of this study was to describe the clinical and angiographic features of TA at the presentation and during the course of the disease in children and adolescents, in order to improve our knowledge about this disease in our population, thus making easier its diagnosis and preventing irreparable vascular damage.

Patients and methods

This is a Brazilian multicenter study on clinical, angiographic and therapeutic characteristics of patients aged under 19 years with a diagnosis of TA. Data collection was carried out between the 2010 and 2011 through a search of medical records.

Centers involved

Fifteen Brazilian tertiary medical centers of reference in Pediatric Rheumatology were invited to participate in this study. Centers with at least three patients with juvenile-onset TA who fulfilled the classification criteria of the disease[10] were included. The study included 10 Brazilian centers of three different geographic regions, including the coordinating center.

Participating patients

Patients with incomplete relevant data were excluded (2 patients). The study included 71 patients followed between 1988 and 2011 with a diagnosis of juvenile-onset TA. The diagnosis was established based on clinical findings and angiographic images compatible with the disease, with exclusion of other possible causes; and all patients met the classification criteria for pediatric Takayasu's arteritis.[10]

Questionnaire

A detailed questionnaire containing demographic, clinical, laboratory, angiographic and therapeutic data was applied. These data were collected at three different time points, in order to allow a longitudinal follow-up of patients, making easier the data collection by the head of each participating center. The questionnaire was composed of 4 Excel® spreadsheets divided as follows: baseline assessment (referring to data from the onset of symptoms to diagnosis establishment); a second evaluation (for data collected between the 6th and 12th month of diagnosis); final assessment (referring to data of the last visit and last examination); and treatment (referring to therapy performed during follow-up). This questionnaire, along with a Word® document with explanations of how to properly fill out the information and standardize the responses, was emailed by the coordinating center to the doctors responsible for each participating center.

Patients were classified according to disease activity in the last six months of the final evaluation: disease in activity, in remission, or death. As there are no validated criteria for defining disease activity for pediatric patients to date, we defined "disease activity" as the presence of characteristic clinical symptoms/signs of the disease and/or laboratory changes (increases in erythrocyte sedimentation rate [VHS] and C-reactive protein [CRP], with exclusion of other possible causes for increases in inflammatory tests) in the last six months; and "remission" as the absence of clinical signs/symptoms and of laboratory changes in the last 6 months of follow-up, with or without pharmacological care. The angiographic examinations were not considered for the evaluation of disease activity, due to the large number of participating centers with different imaging modalities (conventional angiography, CTA and MRA) and also due to the large number of radiologists interpreting the images.

Angiographic types were defined according to Hata's angiographic classification, developed at the International TA Conference in Tokyo in 1994, as shown in Fig. 1.[11]

The study was approved by the Ethics Committee of the coordinating institution and by the other Committees of the participating centers.

Results

Of the 71 patients selected for the study, 51 (71.8%) were girls. At the onset of the disease, 36 patients (50.7%) were children – younger than 10 years; and 35 (49.3%) were teenagers – aged 10–19 years, according to the definition of the World Health Organization. The mean age at onset of symptoms was 9.2 years (±4.2). The means for time to diagnosis and progression time of the disease were 1.2 (±1.4) years and 5.4 (±3.7) years, respectively. At the end of the study, 20 patients were with their disease in activity, 39 in remission (of these, 11 were using corticosteroids), and 5 died (Table 1). Time till death since the onset of follow-up was one, two, six and 44 months, respectively (this information was not available for one patient). The causes of death were heart failure, kidney failure and surgical complications, and we could not identify the *causa mortis* of two patients.

Clinical findings

Constitutional symptoms – fever, asthenia and weight loss – occurred in 77.5% of patients and were the predominant symptoms at the baseline assessment, followed by neurological – headache, stroke, and syncope (70.4%) and musculoskeletal – arthritis, arthralgia, and limb pain (64.8%) symptoms; in the second evaluation, the most frequent symptoms were musculoskeletal (42.2%), followed by neurological (35.9%) and constitutional (32.8%) symptoms; and in the final evaluation, a predominance of neurological symptoms (22.7%) was found,

Table 1 – Clinical and demographic features of patients with juvenile-onset Takayasu's arteritis.

Clinical and demographic features *n* = 71	*n* (%)
Girls, *n* (%)	51 (71.8)
Age at onset mean (SD), years	9.2 (±4.2)
Time to diagnosis mean (SD), years	1.2 (±1.4)
Time of progression mean (SD), years	5.4 (±3.7)
Disease progression at the end of study	
Activity, *n* (%)	20 (31.3)[a]
Remission, *n* (%)	39 (60.9)[a]
In use of corticosteroids	11 (28.2)
No steroids	28 (71.8)
Death, *n* (%)	5 (7.8)[a]

n, number of patients.

[a] Values for 64 patients, because in seven we were not able to assess the presence or absence of disease activity.

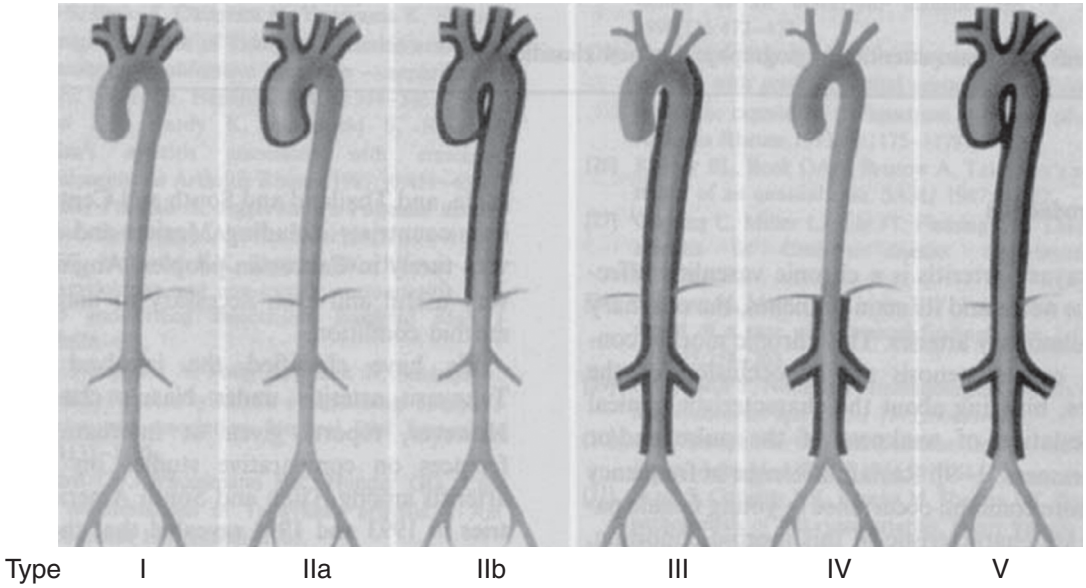

Fig. 1 – Hata's angiographic classification.[11]

followed by musculoskeletal – arthritis, arthralgia, and limb pain (19.7%) and constitutional/gastrointestinal (6.1% each) symptoms (Table 2).

The most frequent cardiovascular signal was a decrease/absence of peripheral pulses in the three evaluation periods, followed by high blood pressure in the first evaluation and by a blood pressure difference in the second and third evaluations (Table 2).

Laboratory findings

Regarding laboratory tests, ESR elevation was the most frequent finding in all three evaluations, being present in over 80% of patients at baseline assessment, with normalization of its value in the majority of patients during follow-up. Tuberculin skin test was performed in 58 patients, and 25 (43.1%) of them tested positive (Table 2).

Table 2 – Clinical and laboratory data of patients with juvenile-onset Takayasu's arteritis at the three assessment time points.

Clinical and laboratory findings	Initial assessment (71) *n* (%)	Second assessment (65)[a] *n* (%)	Final assessment (66)[a] *n* (%)
Constitutional	55 (77.5)	21/64 (32.8)	4 (6.1)
Neurological	50 (70.4)	23/64 (35.9)	15 (22.7)
Musculoskeletal	46 (64.8)	27/64 (42.2)	13 (19.7)
Gastrointestinal	41 (57.7)	14/64 (21.8)	4 (6.1)
Dyspnea/chest pain	38 (53.5)	11/64 (17.2)	3 (4.5)
Visual changes	15 (21.1)	4/64 (6.2)	3 (4.5)
Limb claudication	26 (36.6)	19/64 (29.7)	10 (15.2)
Decrease/absence of pulses	61 (85.9)	51/64 (79.7)	44 (66.7)
Hypertension	60 (84.5)	41/64 (64.0)	29 (43.9)
Heart and arterial bruit	53 (74.6)	43/63 (68.3)	37 (56.1)
BP difference between limbs > 10 mmHg	48 (67.6)	36/51 (70.6)	40 (60.6)
Heart failure	13 (18.3)	3/64 (4.7)	0 (0.0)
Increase of VHS	54/67 (80.6)	40/62 (64.5)	20/60 (33.3)
Anemia	35/70 (50.0)	12/64 (18.8)	8/61 (13.1)
Leukocytosis	41/69 (59.4)	21/64 (32.8)	5/61 (8.2)
Thrombocytosis	30/67 (44.8)	12/63 (19.0)	2/59 (3.4)
PPD +	25/58 (43.1)	7/26 (26.9)	3/17 (17.6)

ESR, erythrocyte sedimentation rate; PPD, purified protein derivative.
Constitutional symptoms: fever, asthenia and weight loss; neurological symptoms: headache, stroke, syncope; musculoskeletal symptoms: arthritis, arthralgia, limb pain; gastrointestinal symptoms: abdominal pain, diarrhea, vomiting; visual change: conjunctival hyperemia, visual blurring, blindness, decreased visual acuity, uveitis.

[a] 6 patients were lost to follow-up after the diagnosis and one of them returned after 5 years.
Note: One patient lacked second evaluation data.

Table 3 – Angiographic classification of patients with juvenile-onset Takayasu's arteritis, according to Hata's classification.[11]

Angiographic classification	*n* (%)
Type I	8 (11.9)
Type IIa	4 (6.0)
Type IIb	1 (1.5)
Type III	9 (13.4)
Type IV	27 (40.3)
Type V	18 (26.9)

The frequency of angiographic types described was related to 67 patients, considering that four patients lacked full initial angiographic data.

During the baseline assessment, 47 patients underwent conventional angiography, 34 MRA and 16 TCA. Imaging tests were not performed on a considerable number of patients in the second and third evaluations; in view of that, only the first studies were evaluated. According to the study of images taken at baseline, a change in abdominal aorta was the most frequent finding, and was present in 67.2% of patients, followed by renal arteries (55.2%) and by subclavian arteries and descending thoracic aorta (26.9% each); The most frequent type of arterial injury was stenosis (89.6%) followed by obstruction (28.4%), swelling (17.9%) and aneurysm (14.9%); and the most frequent angiographic type was type IV, followed by type V (Table 3). There was no significant difference with respect to angiographic types among children and adolescents when types I, IIa and IIb were gathered in a group, and types III and IV in another group, being subsequently compared among themselves and against V group ($p = 0.624$).

As to drug therapy performed by patients during follow-up, the majority (90.0%) made use of oral glucocorticoids, or in the form of pulse therapy. Sixty-one (85.9%) patients used other immunosuppressive drugs (methotrexate, cyclophosphamide, azathioprine and mycophenolate) and only four have used biological therapy (infliximab). Thirty patients (42.3%) used methotrexate and 18 (25.4%) used cyclophosphamide as initial immunosuppressive medication. Of the 25 patients with a positive tuberculin skin test, 10 (40.0%) required the introduction of triple therapy due to a strong suspicion of tuberculosis (clinical findings, chest radiography, bacilloscopy, or biopsy or sputum culture), nine (36.0%) used isoniazid for treatment of latent tuberculosis, and two (8.0%) had been treated for latent tuberculosis infection, and were treated with triple therapy at different follow-up times. Four (16.0%) patients, who were weak reactors, did not undergo treatment with triple therapy nor for latent TB. Two patients with a negative result for tuberculin test underwent treatment for tuberculosis (1) and for latent tuberculosis (2), in the face of their positive epidemiology. Twenty-seven patients (38.0%) underwent some kind of interventional therapy, and angioplasty was the most performed procedure, in 21 (77.8%) of these patients. At the end of this study, the disease evolution in the group of patients who underwent surgical procedures was as follows: 7 (25.9%) were in a state of disease activity, 16 (59.3%) were in remission, and 2 (7.4%) had evolved to death. Two (7.4%) of these patients had no data available (Table 4).

Table 4 – Pharmacological and interventionist therapy carried out during follow-up of patients with juvenile-onset Takayasu's arteritis.

Treatment	Total, *n* (%)
Corticosteroids	64/71 (90.1)[b]
Methotrexate	52/71 (73.2)
Cyclophosphamide	36/68 (52.9)[b]
Azathioprine	7/63 (11.1)[b]
Mycophenolate	3/66 (4.5) [b]
Infliximab	4/64 (6.3)[b]
Antiplatelet	36/68 (52.9)[b]
Anticoagulant	7/65 (10.8)[b]
Antihypertensive	58/70 (82.9)[b]
Latent TB treatment[a]	13/67 (19.4)[b]
TB treatment[a]	13/52 (25.0)[b]
Angioplasty with or without stent	21/71 (29.6)
Bypass	10/71 (14.1)
Nephrectomy	5/71 (7.0)

[a] One patient was treated for latent tuberculosis (TB) and for tuberculosis in different times during the monitoring.
[b] Most percentages were calculated with different denominators, according to the questionnaire data of each patient.

Discussion

This study was conducted in a mixed-race country, with large geographic dimensions and with a large number of patients with juvenile-onset TA. This allowed us a better knowledge of the disease in this age group. We observed a high number of patients under 10 in our series and a high frequency of constitutional symptoms at presentation of the disease.

The predominance of females in our study is consistent with studies in different populations, both in the pediatric population, where this frequency varies between 58 and 83%, as in the adult population, that shows an even higher proportion of women.[4,5,12–16] The high number of children under 10 years in this study, which included patients up to 18 years of age at diagnosis, draws attention and differs from Park et al. series, where 108 children and adults with TA were evaluated.[14] In this study, children up to 10 years at diagnosis accounted for 6.5% of all patients, and adolescents aged between 10 and 20 years accounted for 19%. The mean age at disease onset was also lower than that found in some studies, where this mean reached up to 14 years, but higher than the mean found by Hahn et al. in 31 children of South Africa (8.4 years).[5,12,13] We could not justify the variation in age among the different populations; thus, we hypothesized that genetic and environmental factors may influence the earlier onset of the disease in some regions. The mortality rate of 8% found in our cohort was similar to that in other studies on pediatric populations (range: 7–22%).[6,12,13] Our patients died in a short time, which reflects the severity of this vasculitis.

Constitutional symptoms were present in almost 80% of our patients early in the disease and this percentage could be even higher, if we had included headache in this set of symptoms, taking into account that headache can be part of the inflammatory process of the disease, in the absence of cerebral vessel commitment. As expected, during the patients' follow-up these symptoms were less and less observed, reflecting a

lower degree of inflammation of the disease after its treatment. Other studies also showed these symptoms in people with juvenile-onset TA, but their assessment was carried out separately: fever was present in 4–26% of patients; loss of weight in 4–47.5%; and fatigue (which was evaluated in a recent US study), occurred in 38% of patients at the presentation of the disease.[4,5,12,13] The high frequency of constitutional symptoms in the presentation of TA is a well-known fact, particularly in pediatric populations; and because of their nonspecific character, this causes a delay in diagnosis, which in some patients meant a 4-year setback.

Neurological symptoms were also very prevalent in our series, with improvement during follow-up, similarly to cardiovascular signs (lower peripheral pulses and blood pressure), findings consistent with the literature.[4,6,12,13,17] The decreases in peripheral pulses and blood pressure, especially the first of these signs, did not show significant improvement during follow-up, as these are secondary manifestations of structural arterial changes, a thing hardly modifiable with therapy.

VHS elevation was the most frequent laboratory finding in all three evaluations, reaching 80% of patients at the presentation of the disease, which is consistent with the high rate of increase in inflammatory markers found in other studies in pediatric patients.[5,12,17] Another frequent laboratory finding in our patients was a tuberculin skin test positivity, which was also found in other populations with TA where tuberculosis (TB) is endemic, such as Mexico and South Africa.[12,18] The high frequency of TB found in our children was much higher than that reported in healthy Brazilian children by the Brazilian Institute of Geography and Statistics, thus showing an association between *Mycobacterium tuberculosis* and TA.[19] It is still unclear the relationship between TB and TA, but one explanation is that the heat shock protein 65-kDa found in mycobacteria cross-react with the homologous protein present in the vascular wall of the host, triggering an immune response.

Regarding angiographic changes, stenosis was the most prevalent type of injury, being found in most patients; this finding is consistent with studies on adults and children, where this is the predominant type of injury.[4,15] The frequency of aneurysms found in our patients was higher than the related in studies based on adult populations, ranging between 5 and 12%.[14,15,20,21] The abdominal aorta and renal arteries were the most affected arterial segments, a finding in line with other studies conducted in children.[4,13,17,22] The recent study by Szugie et al. found a higher frequency of involvement of the abdominal aorta and descending thoracic aorta; but the renal arteries were analyzed separately, and possibly their frequency would change if they had been analyzed together.[5] With respect to angiographic type, the most common was type IV, followed by type V, a finding a little different from that in Indian children, where there was a higher prevalence of type V, followed by type IV. On the other hand, our findings are similar to those in children in South Africa, where infradiafragmatic commitment (corresponding to type IV) was the most predominant finding, followed by diffuse involvement (corresponding to type V).[12,13] Angiographic types presented by adolescents were evaluated separately from the types presented by children; thus, we intended to see if there was more likeness with the distribution in adults, in whom types I and V account for virtually all cases.[16] However, the difference between our adolescents *versus* adults remained.

The vast majority of patients needed glucocorticoids and immunosuppressive drugs during follow-up, as shown in other studies, and a significant portion underwent surgery, highlighting the chronic and relapsing nature of the disease.[23] With this treatment, more than 60% of patients were in remission at the end of the study; and this number could possibly be more encouraging with a shorter time to diagnosis.

This study enabled us to analyze a significant number of patients with juvenile-onset TA, making this the largest study in this age group so far. Because of the detailed questionnaire which produced data from three different evaluation periods, we could describe clinical and laboratory characteristics regarding presentation and evolution of TA in our population.

The major limitation of this study stemmed from its retrospective nature and from the large number of evaluators for data collection, as well as the use of different radiologists for interpretation of the angiographic images taken. To minimize possible discrepancies in assessments from the various centers involved, a Word® document with explanations of how to properly fill out the data and standardize the responses was sent to the doctors responsible for each center.

In our series, that included patients up to 18 years of age, we observed a high number of patients under 10 years and high frequency of constitutional symptoms at TA presentation. These findings confirm the importance of the clinical suspicion with respect to this vasculitis in children and adolescents, when these populations present long-term constitutional symptoms of unknown cause, as well as the importance of checking blood pressure and peripheral pulses in our routine physical examinations.

Conflicts of interest

The authors declare no conflicts of interest.

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