Takayasu arteritis in a Brazilian multicentre study: children with a longer diagnosis delay than adolescents

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ABSTRACT

Objective. *To evaluate and compare demographic, clinical, laboratory and angiographic data of Brazilian children and adolescents with Takayasu's arteritis.*

Methods. *In this Brazilian multicentre, retrospective study which included 10 paediatric rheumatology centres, we identified 71 children and adolescents with Takayasu's arteritis which were diagnosed before their 19th birthday. The patients' demographic, clinical, laboratorial and angiographic data were recorded. The participants were divided into two groups: children, defined by the WHO as younger than 10 years old (group 1: 36 patients) and adolescents, defined as individuals aged 10 to 19 years old (group 2: 35 patients). Features of both groups concerning disease manifestations were compared.*

Results. *A total of 21 (58.3%) patients in group 1 and 30 (85.7%) patients in group 2 were girls (p=0.01). The mean age at disease onset, the mean time to diagnosis, and the mean follow-up time were 5.7 and 12.7, 1.8 and 0.7, 7.2 and 3.6 years, respectively, in groups 1 and 2 (p<0.001, 0.001 and <0.001). At initial evaluation, constitutional symptoms (77.5%) were the most predominant symptoms and decreased peripheral pulses (85.9%) was the most predominant clinical sign without differences between groups. The main laboratory findings were increased erythrocyte sedimentation rate followed by leukocytosis. Anaemia, thrombocytosis and higher platelet levels were significantly more frequent in group 1 (p=0.031, 0.001 and 0.018). Angiographic data were similar in both groups.*

Conclusion. *Children presented more laboratory abnormalities but clinical and angiographic characteristics were similar to those presented by the adolescents. Diagnosis delay is longer in younger patients.*

Introduction

Takayasu's arteritis is a chronic vasculitis that affects the wall of large and medium sized arteries, especially the aorta, its primary branches and the pulmonary artery. It was thought in the past to be a disease predominately affecting young Asian women but is currently known to affect both genders, though most studies report a higher frequency among females (1-7).

In the literature, an increasing number of papers on vasculitis, and particularly Takayasu's arteritis, have been published in the last years (8-10). It is the third most frequent type of vasculitis in childhood. However, because it is a rare disease, there are few studies addressing its prevalence among this age group. Some studies report a frequency between 20% and 32% of patients younger than 20 years old (3, 11, 12). Lupi-Herrera *et al*. observed that 77% of the patients were aged between 10 and 20 years old (1).

Studies report differences in the clinical presentation and prognosis of the disease between children and adults, as well as an important delay in the diagnosis among paediatric patients (1, 4, 6, 11). There are some studies addressing Takayasu's arteritis in the paediatric population, but all studies are from specific services, conducted with a small number of patients who were diagnosed according to adult criteria, which hinders acquiring knowledge concerning the disease during childhood (13-16). The characteristics of the disease among different paediatric age

groups have not been compared so far, which motivated this multicentre study. The objective of this study was to analyse the demographic, clinical, laboratorial and angiographic profile at disease onset up to diagnosis in 71 children and adolescents with Takayasu's arteritis and to verify whether there are differences between the two age groups.

Patients and methods

A retrospective, longitudinal and multicentre study was coordinated by the Division of Paediatric Rheumatology of the Paediatric Department at the Universidade Federal de São Paulo.

Centres participating in the study

Fifteen referral centres in the field of paediatric rheumatology were invited to participate in the study. Each centre was required to have a minimum of three patients with Takayasu's arteritis which were diagnosed before their 19th birthday. Ten Brazilian medical centres (including the coordinating centre – Universidade Federal de São Paulo) from three different geographic regions were included in the study.

Patients participating in the study

Those whose data were not properly completed in their medical charts were excluded from the assessment (2 patients). Seventy-one patients were selected from 1988 to 2011. All participants met recently validated classification criteria for Takayasu's arteritis in children, while other causes of arterial insufficiency were excluded (17).

Questionnaire

A questionnaire was administered to address demographic, clinical, laboratorial and angiographic data of patients at initial evaluation (from the beginning of symptoms up to the diagnosis), at follow-up (from the 6th to the 12th month after the diagnosis) and at final evaluation (concerning the last consultation and last exams) and the data concerning treatment and outcome was assessed.

The disease status was characterised at the end of the study as "active", "in remission" or "death". Since there is no validated tool to evaluate the disease activity of Takayasu's arteritis in childhood we defined the disease as active when the patient remained in clinical activity (systemic symptoms and/or worsening signs of vascular insufficiency) and/or laboratorial activity (increase of acute phase proteins) (18). Other possible causes of increasing phase reactants had to be excluded. The disease was considered to be in remission when patients had not been in clinical or laboratory activity during the last six months, whether using medication or not. Angiography or other imaging modalities were not considered for the assessment of the disease progression due to the large number of participating centres with different imaging methods and different radiologists interpreting results.

The angiographic type was classified according to the angiographic classification provided by the International Conference of Takayasu's arteritis in Tokyo (1994) (19).

The 71 patients were divided into two groups according to their age at symptoms onset: children, defined by the World Health Organisation (WHO) as those younger than 10 years old – group 1; and adolescents, defined by the WHO as individuals aged 10 to 19 years old – group 2. The demographic, clinical, laboratorial, and angiographic characteristics at initial evaluation were assessed in both groups.

The study was approved by the Institutional Review Board at the coordinating institution and from the other participating centres.

The SPSS programme, version 20.0 was used for the statistical analysis. The categorical variables were described in terms of percentages and the chi-square test and Fisher's exact test were used to analyse differences between the groups. The continuous variables were described in terms of averages and medians while Student's *t*-test and the Mann-Whitney test were used, in dependency on the normality of the variables to verify differences between groups.

Results

Fifty-one (71.8%) of the 71 participants were girls; 29 (49.2%) were Caucasians, two (3.4%) were Asians, and 28 (47.5%) participants were neither Caucasian nor Asian. Twelve patients provided no information concerning race. The mean age at disease onset was 9.2±4.2 years, with a variation between 4 months and 17.2 years. The mean time to diagnosis was 1.2±1.4 years, with a variation between 0 months and 6 years. The mean follow-up time was 5.4±3.7 years, with a variation between two months and 14.3 years. A total of 36 patients (50.7%) were children (group 1) and 35 (49.3%) were adolescents (group 2) at disease onset. Ten (14.1%) patients were incorrectly diagnosed as having infection at the onset of their disease.

A total of 21 patients of 36 (58.3%) in group 1 and 30 of 35 (85.7%) in group 2 were females, with a significant difference between the groups (p=0.010). Caucasians were predominant in group 1 (53.8%) and non-Caucasians and non-Asians (51.5%) predominated in group 2, though without any statistical difference. The mean age at symptoms onset, time up to the diagnosis, and follow-up time in groups 1 and 2 were 5.7 and 12.7; 1.8 and 0.7; 7.2 and 3.6 respectively with statistically significant differences (Table I).

The most frequent symptoms reported by the patients at initial evaluation were constitutional symptoms such as fever, adynamia, and weight loss, experienced by 55 (77.5%) patients, followed by neurological symptoms, experienced by 50 (70.4%) patients. Six children presented stroke that was confirmed with CNS imaging. The most prevalent signs at initial evaluation were reduced peripheral pulse in 61 (85.9%) patients and hypertension in 60 (84.5%) patients. There were no statistical differences between the clinical manifestations of both groups (Table II).

Most patients from both groups experienced anaemia, leukocytosis, and increased erythrocyte sedimentation rate (ESR) at initial evaluation. The most frequent laboratory alterations were increased ESR and leukocytosis. Anaemia and thrombocytosis were significantly more frequent in group 1; though when the absolute values of haemoglobin and platelets were compared only the level of the last parameter was significantly higher in this group (Table II).

A total of 61 patients underwent a tuberculin test. Of these, 25 (41%) were reactants: 12 were in group 1 and 13 in group 2. Of the 25 positive tests, 22 were strong reactors and three were weak reactors. Thirteen had to start on triple anti-tuberculosis therapy due to a strong indication for Tuberculosis (clinical features, chest x-ray, positive acid fast bacilli or culture in sputum or biopsy) while the others were treated with isoniazide for latent tuberculosis infection.

At initial evaluation imaging exams from the patients in group 1 were: 28 conventional angiographies, 18 magnetic resonance angiography (MRA) and eight computed tomography angiographies (CTA). The imaging exams undertaken by the patients in group 2 on the same occasion were: 19 conventional angiographies, 16 MRA, 8 CTA, one computed tomography (CT), and one CT of the renal arteries. Twenty-four children were submitted to ultrasound from each group at initial evaluation and 41 (85.4%) of them were altered.

Forty-five of 67 (67.2%) patients presented changes in the abdominal aorta, which was the artery most frequently affected, followed by the renal arteries, altered in 37 (55.2%) patients. In group 1, alteration in the abdominal aorta was the most frequent (61%), followed by the renal arteries (58.3%), descending thoracic aorta and subclavian arteries (both in 27.8%) and carotid and mesenteric arteries (both in 19.4%). In group 2, the abdominal aorta was also the most frequently affected (71.9%) followed by the renal arteries (50%), mesenteric arteries (34.4%) and subclavian arteries and descending thoracic aorta (both in 25%). No statistical difference was found concerning arterial involvement between the two studied groups.

The most frequent angiographic type at initial evaluation of both groups was type IV present in 27 of the 67 (40.3%) patients, followed by type V, present in 18 (26.9%) patients. There were no data for the angiographic classification of one patient in group 1 and of three patients in group 2. The initial angiographic classification of each group is presented in Table III. No statistical differences were found between groups 1 and 2 when we gathered types I, IIa and IIb in one group and types III and IV in another group and compared them to each other and also in relation to type V (p=0.624).

The most frequent arterial lesion in group 1 and 2 respectively was: stenosis in 80% and 87.5% followed by obstruction in 25.7% and 31.3%, dilatation/aneurysm in 14.3% and 21.9%, thickening in 14.3% and 3.1%, irregularity in 5.7% and 6.3% and aorta coarctation in 8.6% and 3.1%.

Almost all patients (90.1%) used corticosteroids in the follow-up and the majority needed to use an immunossupressive drug: 73.2% used methotrexate; 52.9% intravenous cyclophosphamide, of which 1 patient also used oral cyclophosphamide, 11.1% azathioprine, 6.3% infliximab and 4.5% mycophenolate. Eighty-three percent used antihypertensive agents, 52.9% used antiplatelet agents and 10.8% used anticoagulants. In relation to interventional therapy, 14.1% underwent angioplasty with stent, 21% angioplasty without stent, 15.9% bypass, 4.8% endarterectomy and 7% nephrectomy. There was

Table I. Demographic and clinical data of Takayasu's arteritis in patients from the groups 1 and 2.

Features	Group 1 n (%) (children) n=36	Group 2 n (%) (adolescents) n=35	p-value
Females n (%)	21 (58.3)	30 (85.7)	0.01*
Ethnicity n (%)			0.798
Caucasians	14 (53.8)	15 (45.5)	
Asians	1 (3.8)	1 (3.0)	
Non-Caucasians / non-Asians	11 (42.3)	17 (51.5)	
NR	10	2	
Age at disease onset (years) mean (SD)	5.7 (±2.1)	12.7 (±2.3)	<0.001*
Time to diagnosis (years) mean (SD)	1.8 (±1.7)	0.7 (±0.7)	0.001*
Follow-up time (years) mean (SD)	7.2 (±4.1)	3.6 (±2.2)	<0.001*

n: number of patients; NR: not related; SD: standard deviation; *p-value <0.05.

Table II. Initial clinical and laboratory results of Takayasu's arteritis in patients from the groups 1 and 2.

Clinical and laboratorial results	Group 1 n (%) (children) n=36	Group 2 n (%) (adolescents) n=35	p-value
Constitutional symptoms	27 (75.0)	28 (80.0)	0.614
Neurological symptoms	24 (66.7)	26 (74.3)	0.482
Musculoskeletal symptoms	25 (69.4)	21 (60.0)	0.405
Gastrointestinal symptoms	19 (52.8)	22 (62.9)	0.390
Cardiovascular symptoms	19 (52.8)	19 (54.3)	0.899
Visual alterations	10 (27.8)	5 (14.3)	0.164
Hypertension	30 (83.3)	30 (85.7)	0.782
Decreased pulse	32 (88.9)	29 (82.9)	0.477
Differences in BP	23 (63.9)	25 (71.4)	0.519
Heart and vascular murmur	27 (75.0)	26 (74.3)	0.780
Claudication	13 (36.1)	13 (37.1)	0.928
Congestive heart failure	7 (19.4)	6 (17.1).	0.802
Anaemia	22/35 (62.9)	13/35 (37.1)	0.031*
Hb values† g/dl	10.8	11.1	0.151
Leukocytosis	22/35 (62.9)	19/34 (55.9)	0.555
Leukocyte value† cells/ml	14.000	12.470	0.466
Thrombocytosis	22/34 (64.7)	8/33 (24.2)	0.001*
Number of platelet† cells /ml	499.000	440.000	0.018*
Increased ESR	28/34 (82.4)	26/33 (78.8)	0.712
ESR value† mm/hour	52	46	0.807

BP: blood pressure; Hb: haemoglobin; ESR: erythrocyte sedimentation rate.
Reference values: Hb ≤11g/dl; Leukocytosis: Leukocytes ≥12,000/ml; High platelets levels: Platelet ≥450,000/ml; increased ESR: ESR ≥20mm/1st hour. †Value in median; *p-value<0.05.

Table III. Initial angiographic classification of patients from groups 1 and 2 according to the International Conference of Takayasu's arteritis in Tokyo, 1994.

Angiographic classification	Group 1 n (%) (children) n=35	Group 2 n (%) (adolescents) n=32
Type I	5 (14.3)	3 (9.4)
Type IIa	1 (2.9)	3 (9.4)
Type IIb	1 (2.9)	0 (0)
Type III	6 (17.1)	3 (9.4)
Type IV	11 (31.4)	16 (50)
Type V	11 (31.4)	7 (21.9)

n: number of patients.
Angiographic Classification [19]: Type I: involves primarily the branches from the aortic arch; Type IIa: involves the ascending aorta, aortic arch and its branches; Type IIb: involves the ascending aorta, aortic arch with its branches and thoracic descending aorta; Type III: involves the thoracic descending aorta, abdominal aorta and/or renal arteries; Type IV: affects only the abdominal aorta and/or renal arteries: Type V: affects the combined features of both type IIb and IV.

no statistical difference in relation to the clinical and interventional treatments applied in the two groups of patients during the progress of the disease.

At the final evaluation, 23 of the 33 (69.7%) patients in group 1 and 16 of the 31 (51.6%) patients in group 2 were in remission. The disease was active in seven (21.2%) patients in group 1 and in 13 (41.9%) patients in group 2. Three (9.1%) patients in group 1 and two (6.5%) patients in group 2 died. The causes of death were heart failure, renal insufficiency, and surgical complications. The cause of death was not defined for two patients. The time of diagnosis up to death ranged from one to 44 months. There was no report on disease status in three patients in group 1 and in four patients in group 2.

Discussion

Takayasu's arteritis is a rare disease with great diagnostic difficulty in all age groups, particularly in childhood, resulting in an important diagnosis delay, especially in Western countries (1, 4). This study reveals a large number of children and adolescent patients with similar clinical and angiographic characteristics, though the first group presented a greater frequency of laboratory alterations and longer diagnosis delay.

We observed a larger proportion of girls, which is comparable to other studies addressing paediatric populations reporting a frequency of females ranging from 58% to 83% (10-24). We found a similar ethnicity to the one observed in the general Brazilian population according to the last census (25).

There was an average delay of 1.2 years prior to diagnosis, which is a shorter period than that found by Vanoli *et al*. when assessing children and adults with Takayasu's arteritis in Italy, where an average delay of 46 months and a median of 15.5 months was found (4). The time until diagnosis in our study was, however, longer than that found in a study conducted with 24 Indian children, which reported an average of only four months between the onset of symptoms and the diagnosis (22). Since the clinical manifestations of the disease were similar in the three populations, we believe this variation in the time to diagnosis may be explained by the different frequencies in which the disease affects each population.

The constitutional and neurological symptoms, reduced peripheral pulses and hypertension, were the most prevalent manifestations in the initial phase of the disease, which is in agreement with the paediatric literature (20-22, 24, 26). The laboratory finding most frequently found among our patients was increased ESR, which is also reported in other studies of children (21, 22).

When the demographic characteristics of the two groups were compared, a larger percentage of girls was observed in group 2, composed of adolescents. This result is probably due to the hormonal influence in the development of auto-immune diseases. Almost all studies report a higher frequency of females, especially studies conducted with adults; some report a frequency of females greater than 90% (1, 2, 4-7). Only some studies conducted in India report a similar frequency in both sexes (27, 28).

Children presented a longer delay to diagnosis compared with adolescents, with a significant difference. Previous studies reported that children had a longer delay in diagnosis when compared to adults (6, 11). An Italian study conducted with 104 patients showed that being 15 years old or younger at the symptoms onset was an independent predictive factor for a diagnosis delay of longer than two years (4). Since we did not find differences in the clinical presentation of the two groups to explain such results, we presume that this delay for diagnosis in group 1 is due to physicians failing to recognise the disease, in addition to a greater number of potential differential diagnoses in younger patients. Additionally, since Takayasu's arteritis is an insidious disease and constitutional symptoms are frequent in the initial phase, it is common for children to receive a diagnosis of recurrent infectious disease, since these are very prevalent among younger children.

No differences were found in relation to clinical characteristics between the two groups of patients. Lupi-Herrera et al observed in 1977 that the disease onset was more acute among patients younger than 15 years old and that 67% of them experienced heart failure (1). A few studies, however, described a more insidious disease, with less specific symptoms and a higher incidence of systemic manifestations in children when compared to adults (8, 29, 30).

A greater frequency of haematological alterations was observed in this study, which may reflect a greater inflammatory response in children. Similar to our findings, Lupi-Herrera *et al*. found greater inflammatory alteration in younger patients and increased ESR among individuals under 15 years of age (1).

A high incidence of positive tuberculin skin tests was found, similar to other studies conducted with populations in which tuberculosis is endemic, such as Mexico and South Africa (1, 21). This incidence was much higher than the

one found in 42 healthy Brazilian children in a referral centre of Infectology in São Paulo where 7% of this population had positive tuberculine skin tests. The incidence of tuberculosis infection in our study was also much higher than that described in Brazilian children (25). The exact mechanism of such an association is unknown, but one of the explanations is the presence of the acute shock protein (65-kd HSP) found in micobacteria, which has a cross-reaction with the homologous protein present in the host's vascular wall, triggering an immune response (31).

The abdominal aorta was the arterial segment most affected in our patients, followed by the renal arteries. In contrast with studies on adults, in which there is an important involvement of the aortic arch and branches, these are also the most involved arteries in children in other populations (20, 22, 24, 32). Arterial stenosis was present in 80% of our patients and was much more frequent than other types of lesions. Stenosis is also the most frequent type of arterial lesion in other studies conducted with children and adults, which is the lesion characteristic of Takayasu's arteritis (8, 24). A low frequency of thickening was found at initial phase of the disease, perhaps because most patients underwent conventional angiography in their initial assessment where this alteration cannot be observed.

The angiographic type IV of the disease was the most frequently found in our patients at disease onset followed by type V, slightly different from the study conducted in India, which showed a greater frequency of type V, experienced by 63% of the children, followed by type IV (29%) (22). A study conducted with 31 children in South Africa reported a greater frequency of infra diaphragmatic involvement (35%) and diffuse involvement (35%), corresponding to types IV and V, respectively, according to the new classification (19). Studies with Brazilian adult patients reported a greater frequency of angiographic type V followed by type I (7, 33). Although ultrasound is not a validated imaging exam in the classification criteria it was useful in the first diagnostic phase since it was altered in most patients.

To the best of our knowledge, this is the largest study described in the literature that systematically evaluated a broad clinical and laboratorial protocol for children and adolescents with Takayasu's arteritis. It has the advantage of being a multicentre study conducted in a racially diverse country in which three different geographic regions were included: five states and 10 tertiary paediatric rheumatology referral centres. It is also the first study to use classification criteria validated for Takayasu's arteritis in the paediatric age group.

A limitation of this study is the fact that it is a retrospective study, with different evaluators compiling data and different radiologists interpreting images. In order to minimise errors, evaluators were instructed on how to correctly record the data.

Even though most studies report that the peak incidence of Takayasu's arteritis occurs between the second and fourth decades, we observed that more than half the children in our study were 10 years old or younger at disease onset. The time to diagnosis among these patients took twice as long as that for adolescents, which reveals a lack of awareness among physicians concerning the presence of this vasculitis in younger patients.

Takayasu's arteritis must be considered in the differential diagnosis of children and adolescents with a recurrent fever or other prolonged unspecific systemic symptoms associated with increase of acute phase proteins, regardless of age. A complete physical exam verifying the peripheral pulse and blood pressure of children is required to confirm the diagnostic suspicion. In the follow-up manifestations of heart involvement, stroke, visual impairment, or claudication are suggesting features of the disease.

Because this is a rare disease, international multicentre and prospective studies are needed to better characterise Takayasu's arteritis among paediatric patients.

In conclusion, children presented more laboratory abnormalities but clinical and angiographic characteristics were similar to those presented by the adolescents. Diagnosis delay is longer in younger patients.

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