

Childhood-Onset Takayasu Arteritis: A Single-Center Experience

Childhood-Onset Takayasu Arteritis

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Abstract

Aim: This study aimed to catalogue and describe the clinical manifestations, angiographic findings, and treatments in pediatric Takayasu arteritis (TA) patients. **Materials and Methods:** The files of the patients diagnosed with TA at Dr. Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital, Department of Pediatric Rheumatology, Ankara, Turkey, between 2015 and 2020 who met classification criteria of European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society for childhood-onset TA were retrospectively reviewed. **Results:** The study included 8 patients (6 females and 2 males) with a mean age at onset of the disease of 13.72 ± 2.62 years and a median follow-up time of 24.50 months (range: 2-108 months). The most common complaints were constitutional findings, such as fever, weight loss, and weakness (75%). The most common physical examination findings at presentation were murmur (100%), pulselessness (75%), and hypertension (62.5%). The most common type of angiographic involvement was type V (n=4). The most commonly used immunosuppressive drugs for the treatment of TA were corticosteroids and methotrexate. Remission was achieved based on clinical and laboratory findings in 7 of the 8 patients. None of the patients died. **Discussion:** The present findings show that despite recent developments in the diagnosis and treatment of childhood TA, diagnostic delay remains an important problem. Patients are still commonly diagnosed at the irreversible stage of vascular involvement; therefore, additional well-designed multicenter studies are needed to improve the early diagnosis rate and the administration of appropriate treatment in pediatric TA patients.

Keywords

Takayasu; Arteritis; Vasculitis

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Introduction

Takayasu arteritis (TA) is a rare, granulomatous vascular vasculitis that progresses with exacerbations and remissions, affects the aorta and its branches, and can cause dilatation, stenosis, and/or aneurysm in these vessels [1, 2]. It is most common in East Asian countries, but its precise incidence worldwide remains unknown. Studies conducted in Europe and North America report an estimated annual incidence of 1-3 / 1,000,000. Although it is frequently seen during the 3rd and 4th years of life, cases ranging from infancy to adolescence have been reported [3].

TA is among the most common vasculitides of childhood. Unfortunately, there is no disease-specific diagnostic test, which leads to frequent delays in diagnosis and treatment, especially in children [4]; therefore, vascular involvement is often irreversible by the time it is diagnosed. In addition to diagnostic difficulty, evaluation of disease activity and treatment response are also challenging for clinicians [2]. It is reported that as compared to adults, treatment-resistant TA is more common and remission is less common in children [4]. In addition, data on the clinical features and treatment of TA in children are limited. Therefore, this study aimed to catalogue and describe the clinical manifestations, angiographic findings, and treatments in pediatric TA patients.

Material and Methods

The files of patients diagnosed with TA at Dr. Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital, Department of Pediatric Rheumatology, Ankara, Turkey, between 2015 and 2020 were retrospectively reviewed. The patients were diagnosed according to classification criteria of the European League Against Rheumatism/Paediatric Rheumatology International Trials Organization /Paediatric Rheumatology European Society (EULAR / PRINTO / PReS) [1]. All patients underwent computed tomography (CT) and/or magnetic resonance angiography (MRA). According to EULAR / PRINTO / PReS classification criteria, in order to diagnose TA in addition to positive angiographic findings, patients must meet 1 of the following criteria: (a) systemic arterial hypertension; (b) a blood pressure difference of >10 mm Hg between the right and left arms; (c) a decrease in or lack of peripheral artery pulse (s) or claudication; (d) murmur of the aorta or its main branches; (e) elevated acute phase markers [1].

Patients age, gender, age at diagnosis, age at symptoms onset, symptoms and physical examination findings at presentation, duration of follow-up, treatment, and the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level at the time of diagnosis, and at the last follow-up visit were recorded. ESR \geq 20 mm/hour and CRP \geq 5 mg/L were considered high. Arterial hypertension was defined as blood pressure \geq 95th percentile for that age.

The extent of vascular involvement was classified according to the Numano's angiographic classification system, as follows: type I (involvement of the main branches from the aortic arch only); type IIa (involvement of the ascending aorta, the aortic arch, and its branches); type IIb (involvement of the ascending aorta, the aortic arch, and its branches, and the thoracic descending aorta); type III (involvement of the thoracic

descending aorta, abdominal aorta, and/or renal arteries); type IV (involvement of the abdominal aorta and/or renal arteries); type V (the combined features of types IIb and IV) [5, 6].

Statistical analysis

IBM SPSS Statistics for Windows v.21.0 (IBM Corp., Armonk, NY) was utilized for statistical analysis. Results are given as mean \pm SD for continuous variables with normal distribution. Continuous variables not normally distributed were presented as median (range). Categorical variables were presented as numbers and percentages.

Results

The study included 8 pediatric patients diagnosed with TA, of which 75% (n = 6) were female. The mean age at onset of symptoms and diagnosis was 13.15 \pm 2.68 years and 13.72 \pm 2.62 years, respectively. Whereas median follow-up time was 24.50 months (range: 2-108 months), the median time from onset of symptoms to diagnosis was 5.50 months (range: 1-24 months). Constitutional findings, including fever, weight loss, weakness, and night sweats, was noted in 6 (75%) patients; 1 patient without any symptom was diagnosed with TA due to the presence of a murmur noted during a routine physical examination, and 1 patient was diagnosed after being examined for neck pain at presentation. The patients' demographic, clinical, and laboratory findings are given in the Table 1.

All patients had murmur and elevated acute phase markers at the time of diagnosis. In general, at the time of diagnosis, 6 patients (75%) had pulselessness, 5 (62.5%) had hypertension, 3 (37.5%) had headache, 2 (25%) had a difference in blood pressure > 10 mmHg between the right and left arms, 2 (25%) had joint pain, 2 (25%) had claudication, 2 (25%), had aortic coarctation, and 1 (12.5%) had pulmonary involvement. Cranial involvement developed in 1 patient (25%) during follow-up.

According to the Numano's angiographic classification system, the most common type of angiographic involvement type was type V (n=4), followed by type IIb (n=2), and type I (n=1) and type IIa (n=1). Widespread involvement was present in 50% (n = 4) of the patients at the time of diagnosis. Blood was delivered to vital organs almost only by collateral vessels. The most common vascular abnormality pattern based on angiography was stenosis (80% of all lesions), followed by an increase in arterial wall thickness (60%), occlusion (30%), and aneurysm (10%). The most frequently involved vessels were the arcus aorta (100% [n = 8]), the ascending aorta (87.5% [n = 7]), the descending aorta (75% [n = 6]), the abdominal aorta (50% [n = 4]), and the renal arteries (%25 [n = 2]).

Acute phase markers were elevated at the time of diagnosis in all 8 patients; median ESR values were 89.00 mm/hour (range: 36.0-110.0 mm/hour) and 10.00 mm/hour (range: 2.0-30.00 mm/hour) at the time of diagnosis and at the last follow-up visit, respectively, and median CRP values at the time of diagnosis and at the last follow-up visit were, respectively, 112.5 mg/L (range: 22.0-225.0 mg/L) and 3.3 mg/L (range: 2.1-4.8 mg/L). The most commonly used immunosuppressive drugs used to treat TA were corticosteroids (n=8 [100%]), followed by methotrexate (n=7 [87.5%]), cyclophosphamide (n=4 [50%]), tocilizumab (n=4 [50%]) and adalimumab (n=1 [12.5%]). The patient who received adalimumab treatment had concomitant

Crohn's disease. Clinical and laboratory remission was achieved in all except for 1 patient who was referred to a specialized medical center due to the development of cranial involvement. Angiographically, none of the patients developed new vascular lesions; however, vascular lesions detected at presentation did not improve in any of the patients.

Table 1. Clinical and laboratory features of the TA patients

Females/males, n/n (%/%)	6/2 (75/25)
Mean \pm SD age, years	16.73 \pm 4.31
Mean \pm SD age at diagnosis, years	13.72 \pm 2.62
Mean \pm SD age at onset of symptoms, years	13.15 \pm 2.68
Median diagnostic delay, months (range)	5.50 (1-24)
Median duration of follow-up time, months (range)	24.50 (2-108)
Bruits, n (%)	8 (100)
Elevated acute phase markers, n (%)	8 (100)
Systemic features	
Fever, n (%)	6 (75)
Weight loss, n (%)	6 (75)
Weakness, n (%)	6 (75)
Absent or decreased pulse, n (%)	6 (75)
Hypertension, n (%)	5 (62.5)
Headache, n (%)	3 (37.5)
Difference in blood pressure, n (%)	2 (25)
Arthralgia/arthritis, n (%)	2 (25)
Claudication, n (%)	2 (25)
Aortic coarctation, n (%)	2 (25)
Cranial involvement, n (%)	1 (12.5)
Pulmonary involvement, n (%)	1 (12.5)
Median baseline ESR, mm/hour (range)	89.0 (36.0-110.0)
Median last follow-up ESR, mm/hour (range)	10.0 (2.0-30.0)
Median baseline CRP, mm/hour (range)	112.5 (22.0-225.0)
Median last follow-up CRP, mm/hour (range)	3.3 (2.1-4.8)

Discussion

The present study performed a single-center retrospective review of the clinical, treatment, and angiographic features of 8 children diagnosed with TA. In the present study, TA exhibited a female predominance (75%), as reported earlier [4, 7]. Due to the lack of a specific marker for diagnosing TA, it is difficult to diagnose, and the consequent diagnostic delay is a common problem. Some studies report that the time from onset of symptoms to diagnosis is 2-11 years, and that the delay is longer in children than in adults [8, 9]. In the present study, the median time from onset of symptoms to diagnosis of TA was 5.5 months, although earlier reports vary. A Brazilian study [10] reported a median diagnostic delay of 1.2 years, versus 17 months in the study from England [11]. An earlier study from Turkey reported a median delay of 2.5 months [7].

Diagnosis of TA is made based on angiographic abnormalities of the aorta and/or its major branches, which were in all 8 (100%) patients of the present study's, and \geq 1 of the following 4 features: decreased peripheral artery pulse (s), which was in 6 (75%) patients of the present study; a difference in blood pressure $>$ 10 mmHg, which was in 2 (25%) of the presented patients; murmurs of the aorta and/or its main branches, which was in all 8 (100%) patients; arterial hypertension, which was

in 5 (62.5%) of the presented patients; elevated acute phase markers, which was in all 8 (100%) patients. Similar to previous studies, in the present study constitutional symptoms such as weight loss, weakness, and fever, were observed in 75% of the patients. Sahin et al [7] observed constitutional symptoms in 81.2% of 16 patients and the most common finding (77.5%) was constitutional symptoms in a study from Brazil that included 71 children with TA from 10 centers [10]. The most common physical examination findings in many studies are hypertension, blood pressure difference, and murmur [11, 12]. In the present study, murmur was present in all 8 patients, 75% of the patients had pulselessness, and 62.5% had hypertension, as previously reported. Moreover, all of the present study's patients had elevated acute phase markers at the time of diagnosis.

The most commonly reported types of angiographic involvement in TA are type IV and type V [2, 13-15]. Similarly, in the present study, the most common angiographic involvement was type V, according to Numano's classification [11]. Type III was reported as the most common type only in a study from China [16]. When the aortic segments and branches were evaluated separately, in the present cohort, the arcus aorta was the most frequently affected, followed by the descending and ascending aorta. Some studies reported that the abdominal aorta and renal arteries were the most commonly affected vessels [10-12, 17]. The most common vascular abnormality pattern based on angiography in the present study was stenosis (80% of all lesions), which is compatible with the literature [11, 12].

The primary aim of the treatment of TA is the prevention of irreversible vascular damage and protection of vital organs. Delayed diagnosis is a frequent problem due to the lack of a disease-specific diagnostic test, and because the signs and symptoms of the disease are not specific. Diagnostic delay leads to progress towards the pulsation phase characterized by severe vascular damage, and advanced and serious disease when the diagnosis is finally made [17]. Corticosteroids are the basis of TA treatment. Second-line immunosuppressants, such as methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), and cyclophosphamide (CYC), are used together with corticosteroids [18]. Apart from these conventional immunosuppressants, biological drugs, including infliximab (IFX) and tocilizumab (TCZ), also yield good results [19, 20]. In a North American series remission was achieved in 60% of patients treated with steroids only; however, in many of the patients, relapse occurred when the steroid dose was reduced [21, 22].

To date, there are no evidence-based data demonstrating the superiority of one agent over another in the treatment of TA. Ozen et al. [23] successfully used MTX, which followed CYC and steroid induction. Good results were obtained with AZA and MMF in adult and pediatric TA patients [21-25]. Batu et al. [20] administered TCZ treatment to TA patients that were resistant and achieved remission in all patients. In the present study, all patients received corticosteroid therapy. Overall 4 patients with widespread involvement received high-dose pulse methylprednisolone, whereas the other 4 patients were given steroid treatment 1-2 mg/kg/day. In addition, the 4 patients with widespread involvement were given intravenous CYC together with steroids for induction therapy, whereas the 4 patients

without widespread involvement were given MTX therapy. The CYC usage rate in the present study was 50%, though it varies widely according to earlier reports. For example, a Brazilian study [4] reported that 6% of patients received CYC, versus 62.5% of patients in a Turkish study [7]. The differences in CYC usage might be due to differences in vascular involvement or treatment protocols. Moreover, there is still no consensus concerning the optimal treatment for TA. In the present study, patients with widespread involvement were given TCZ after CYC treatment, and ADA treatment was given to 1 patient with concomitant Crohn's disease. Clinical and laboratory remission was achieved in all except for 1 patient in the present study (who was referred to a specialized medical center due to the development of cranial involvement). Angiographically, new vascular lesions did not develop in any of the patients; however, the vascular lesions already present did not regress. Despite recent advances in the diagnosis and treatment of TA, 4 patients in the present study had extensive vascular involvement at the time of presentation; blood was delivered to their vital organs almost only by collateral vessel. The primary limitations of the present study are its retrospective design and small patient population.

In conclusion, the present findings show that pediatric TA patients are still diagnosed at the stage of irreversible vascular involvement. Thus, additional well-designed, larger scale multicenter studies are needed to improve early diagnosis and administration of appropriate timely treatment courses, especially in pediatric patients. Delayed diagnosis of TA remains an important problem. Based on the present findings, we think that it is necessary to raise awareness of TA among general pediatricians and other physicians, so as to increase the likelihood that patients will be diagnosed before the development of irreversible vascular injury.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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