Takayasu Arteritis in Children

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ABSTRACT. ***Objective.*** To retrospectively evaluate the clinical features, angiographic findings, and outcomes of children with Takayasu arteritis (TA) in Turkey.

Methods. Clinical, laboratory, and angiographic findings and outcomes of 19 children with TA were evaluated with a retrospective chart review. The criteria for inclusion were those proposed by the American College of Rheumatology.

Results. Mean followup period was 35.89 ± 40.75 months (range 1–168, median 30). There were 14 girls and 5 boys. The mean age at diagnosis was 12.84 ± 2.69 years (range 8–17, median 13). The most common complaints on admission were headache (84%), abdominal pain (37%), claudication of extremities (32%), fever (26%), and weight loss (10%). One patient presented with visual loss. Examination on admission revealed hypertension (89%), absent pulses (58%), and bruits (42%). Angiography revealed type I in 13 patients (aortic arch, descending thoracic, and abdominal aorta), type II in 4 (descending thoracic aorta and abdominal aorta), and type IV in 2 (diffuse aortic and pulmonary artery). The most commonly involved vessels were the renal, subclavian, and carotid arteries. All patients received corticosteroid therapy, and further immunosuppressive therapy was added in 15 patients. Fourteen of the 17 hypertensive patients had renal artery stenosis and 9 underwent surgery or interventional therapy. Thoraco-abdominal bypass graft was performed in 2 patients who had abdominal aortic stenosis.

Conclusion. Hypertension is the most common clinical feature at presentation. Corticosteroid and immunosuppressive therapy was effective in the control of disease activity. Angioplasty or bypass grafting was successfully performed when needed. (First Release Mar 15 2008; J Rheumatol 2008;35:913–9)

Key Indexing Terms:
TAKAYASU ARTERITIS PEDIATRIC VASCULITIS HYPERTENSION

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Dr. Duzova was supported by The Turkish Academy of Sciences (Programme to Reward Successful Young Scientists, A.D/TUBA – GEBIP/2006-6).

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Accepted for publication December 15, 2007.

Takayasu arteritis (TA) is a chronic, inflammatory disease of the aorta and its main branches[1]. Its etiology is unknown. The disease is seen predominantly in Asian patients[2]. Females are affected more than males[3]. Although the peak incidence is in the third and fourth decades, children and teenagers may be affected, and infants are rarely affected[3-7].

TA appears to have an acute early phase, with hypertension, headache, fever, muscle pain, arthralgias, night sweats, and weight loss. At this stage there are no specific laboratory abnormalities, and the disease is often unrecognized. If untreated, the disease progresses to a chronic phase with involvement of the aorta and its main branches, in which the patients present with clinical symptoms of limb or organ ischemia[8,9].

Although conventional angiography is the gold standard investigation for the diagnosis and followup of patients, noninvasive methods such as magnetic resonance (MR) angiography and computed tomography (CT) angiography are available for diagnosis[10-12].

Steroids, cyclophosphamide, methotrexate (MTX), azathioprine, mycophenolate mofetil, and anti-tumor necrosis factor (anti-TNF) antibodies along with antihypertensive agents have been recommended for treatment of TA[9,13].

We evaluated clinical, laboratory and angiographic features, treatment modalities, and outcome of childhood TA in Turkey.

MATERIALS AND METHODS

Pediatric nephrology and rheumatology centers in Turkey were invited to participate in the study and were asked to complete a questionnaire for all children ≤ 18 years of age who were diagnosed with TA within the previous 15 years, retrospectively. From January 1992 to December 2006, 19 children with TA from 9 centers were enrolled, based on the diagnostic criteria of the American College of Rheumatology (ACR)[14]. Data from the records included demographic information, family history, clinical features (at time of diagnosis, and during the whole course of the disease), vascular findings, medical and surgical treatment, and outcome. Angiographic findings were classified according to angiographic classifications of Lupi-Herrera, *et al*[15] and Ishikawa, *et al*[16].

Diagnosis of TA by the ACR criteria[14] requires fulfillment of 3 of 6 criteria: (1) age at disease onset ≤ 40 years; (2) decreased peripheral artery pulse(s); (3) claudication of extremities; (4) blood pressure difference > 10 mm Hg; (5) bruits over the aorta and/or its major branches; and (6) arteriographic abnormalities of the aorta.

Statistical analysis. Data are summarized as mean, standard deviation, and median for continuous variables and number of subjects for categorical variables.

Table 1. Characteristics of 19 patients with Takayasu arteritis.

Features	
Sex, n (%)	
Female	14 (73.6)
Male	5 (27.4)
Age at diagnosis, yrs	
Mean ± SD (range)	12.84 ± 2.69 (8–17)
Median	13
Delay in the diagnosis, mo	
Mean ± SD (range)	26.37 ± 23.24 (1–60)
Median	12
Followup period, mo	
Mean ± SD (range)	35.89 ± 40.75 (1–168)
Median	30
Diagnosis criteria, n (%)	
Age at disease onset ≤ 40 years	19/19 (100.0)
Decreased peripheral artery pulse(s)	11/19 (57.9)
Claudication of extremities	6/19 (31.6)
Blood pressure difference > 10 mm Hg	11/19 (57.9)
Bruits over aorta and/or its major branches	8/19 (42.1)
Angiographic abnormalities of aorta	19/19 (100.0)

Table 2. Clinical and laboratory features of patients at diagnosis.

Features	
Constitutional/musculoskeletal, n (%)	
Fever	5/19 (26.3)
Arthralgia/arthritis	3/19 (15.8)
Weight loss	2/19 (10.5)
Abdominal pain	7/19 (36.8)
Cardiovascular, n (%)	
Arterial bruit	5/17 (29.4)
Decreased or absent pulse	11/19 (57.9)
Blood pressure difference > 10 mm Hg	11/19 (57.9)
Claudication of extremities	6/19 (31.6)
Hypertension	17/19 (89.5)
Central nervous system, n (%)	
Headache	16/19 (84.2)
Dizziness	7/19 (36.8)
Visual loss	1/19 (5.3)
Laboratory findings, mean ± SD	
Erythrocyte sedimentation rate, mm/hr	60.17 ± 26.97
Leukocyte count, mm^3	9,106 ± 2,451
Platelet count, mm^3	476,714 ± 177,981
Creatinine, mg/dl	0.71 ± 0.24

RESULTS

Patients' characteristics. A total of 19 patients (14 girls, 5 boys) were enrolled. All patients met the diagnostic criteria for TA; 1 patient (5%) met all of the 6 criteria, 5 patients (26%) met 5, 5 patients (26%) met 4, and 8 patients (42%) met 3 criteria (Table 1).

Clinical features and laboratory findings. The main clinical features and laboratory findings of all patients at presentation are shown in Table 2. Positive tuberculin test was found in 3 patients, and one had active renal tuberculosis.

Vascular involvement. Angiography was performed in all patients at diagnosis (conventional angiography in 15 and MR angiography in 4). MR angiography showed vessel-wall thickening in addition to stenosis and occlusions of the vessels (Figure 1). Disease outcome was evaluated with angiography in 11 patients (conventional angiography in 2, MR angiography in 9) who were followed for more than 24 months. The followup period was less than 12 months in 5 patients, and they were evaluated with Doppler ultrasono-

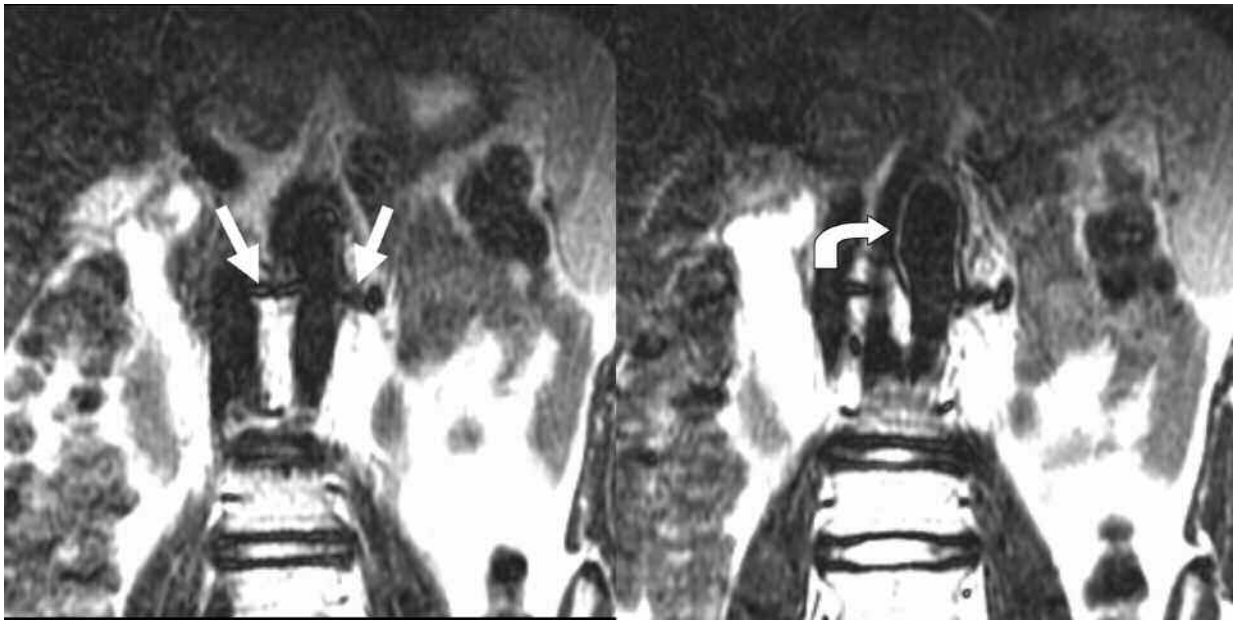


Figure 1. Contiguous T2-weighted coronal MR images show wall thickening. A. Both renal arteries (arrows). B. Abdominal aorta (arrow).

graphy. Two patients were lost to followup (after 2 and 6 months) and 1 patient died at Month 2.

A total of 137 lesions were detected: stenosis was the most common type of lesion, followed by occlusion, dilatation, and aneurysms. The type and distribution of arterial involvement is given in Table 3. The most commonly involved vessels were the renal (14 patients, 25 units), subclavian (11 patients, 20 units), and carotid arteries (10 patients, 17 units). Distribution of involved vessels according to the classifications proposed by Lupi-Herrera, *et al*[15] and Ishikawa, *et al*[16] is shown in Table 4.

Symptoms of limb hypoperfusion (claudication of extremities) were present in 6 patients (31.6%). Raynaud's phenomenon and distal cutaneous hypothermia was seen in only 1 patient (5.3%), who had subclavian artery stenosis.

Headache was the most common complaint of patients

Table 3. Vascular involvement in patients with Takayasu arteritis.

Involved Vessels	Any Lesion*	Type of Lesion, n			
		Stenosis	Occlusion	Dilatation	Aneurysm
Left subclavian artery	11	4	7	1	1
Right subclavian artery	9	6	5	1	1
Left carotid artery	10	8	3	1	—
Right carotid artery	7	4	3	1	—
Aortic arch	5	1	—	4	2
Thoracic descending aorta	9	4	—	3	5
Abdominal aorta	11	9	—	4	4
Pulmonary artery	2	1	1	—	—
Right renal artery	12	10	2	2	—
Left renal artery	13	11	2	3	—
Superior mesenteric artery	9	7	1	1	—
Inferior mesenteric artery	1	—	—	1	—
Celiac trunk	5	5	—	—	—
Left vertebral artery	3	2	1	—	—
Right vertebral artery	3	1	2	—	—
Right superficial femoral artery	1	—	1	—	—
Left superficial femoral artery	1	—	1	—	—
Total (%)		73 (53.3)	29 (21.2)	22 (16.0)	13 (9.5)

* Number does not correspond to sum of single lesion numbers because an artery can be affected by more than one lesion.

Table 4. Distribution of involved vessels according to classification by Lupi-Herrera, *et al*[15] and Ishikawa, *et al*[16].

Type	Affected Vessels	n = 19	n (%)
I	Aortic arch only	1	13 (68.4)
	Aortic arch and descending thoracic aorta	1	
	Aortic arch, thoracic and abdominal aorta	6	
	Aortic arch and abdominal aorta	5	
II	Descending thoracic aorta only	—	4 (21.1)
	Descending thoracic and abdominal aorta	4	
III	Diffuse aortic involvement	—	—
IV	Diffuse aortic and pulmonary artery involvement	2	2 (10.5)

(16/19; 84%). Except for 2, all had hypertension and 9 had carotid or vertebral artery involvement. Seven patients had dizziness (all with hypertension and only 2 with carotid or vertebral artery involvement). Transient ischemic attacks and stroke were not detected. Visual loss was present in only 1 patient (5.3%) with occlusions of vertebral and carotid arteries and respective intracranial segments.

Hypertension was found in 17 of the 19 patients. Blood pressure values (recorded from 4 limbs) at diagnosis ranged from 140/80 mm Hg to 200/180 mm Hg. Fourteen of these patients had renal artery stenosis or occlusion. Two of the remaining 3 patients had narrowing of the aorta and one had abdominal aortic aneurysm.

Seventeen patients underwent echocardiography: 5 patients (5/17; 29%) had aortic valvular insufficiency, 6 (6/17; 35%) had left ventricular hypertrophy, and 2 patients (2/17; 12%) had pericardial effusion. Two patients (2/19; 10.5%) had been diagnosed as having cardiomyopathy before the diagnoses of TA. In addition, 8 patients had been diagnosed with familial Mediterranean fever, acute rheumatic fever, myocarditis, seronegative spondyloarthropathy, and seronegative spondyloarthropathy plus Crohn's disease before the diagnosis of TA. HLA-B27 findings were negative in these patients.

Treatment and outcome. Mean followup period was 35.83 ± 40.75 months (range 1–168, median 30 months). The followup period was less than 1 year in 6 patients, and one patient was lost to followup after 36 months.

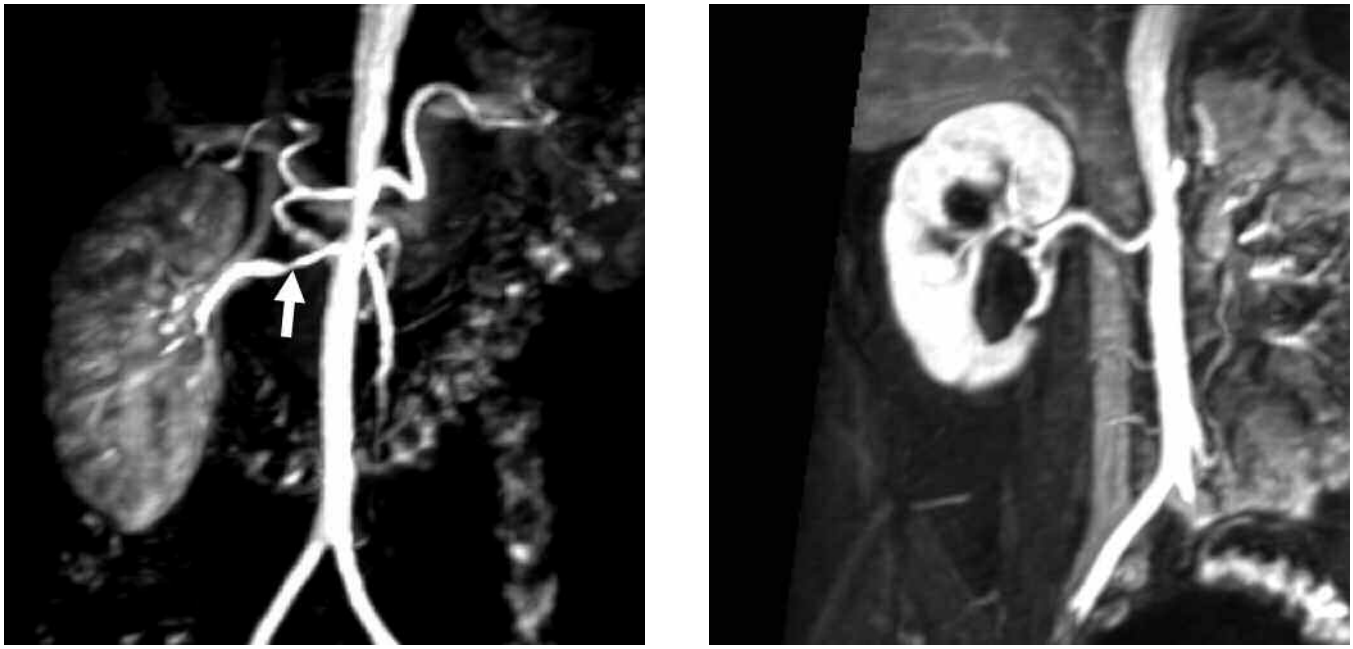
All patients received corticosteroid therapy; the starting dose of prednisolone was 2 mg/kg/day, which was tapered after 1–2 months and was continued with alternate-day dosing at the lowest dose, 5–10 mg/day. Fifteen patients received additional immunosuppressive drugs; out of 10 patients with severe disease (described as widespread involvement or life-threatening disease, i.e., pulmonary artery), 9 received cyclophosphamide (maximum total dose 180 mg) and 1 patient received infliximab. MTX (10–12.5 mg/m^2/week) and azathioprine (2 mg/kg/day) were used as steroid-sparing drug in 11 and 5 patients, respectively.

Eleven patients were followed for a period of ≥ 24 months; although laboratory markers of inflammation showed remission, control angiography of these patients revealed progression of lesions in 4 (36.4%), lesions that remained unchanged in 4 (36.4%), and partially healed lesions in 3 (27.4%). The most distinctive changes were progressive narrowing or occlusion or new stenotic lesions. The patient with pulmonary artery stenosis died within 1 month with pulmonary hemorrhage. Three patients with partially healed lesions (recanalization of the vessel and regression of vessel-wall inflammation) received MTX plus azathioprine/cyclophosphamide, azathioprine plus infliximab, or MTX along with steroids. The patient treated with infliximab was a 14-year-old girl diagnosed with seronegative spondyloarthropathy 4 years before the diagnosis of TA. After diagnosis of TA, treatment with prednisolone 1 mg/kg daily and azathioprine 2 mg/kg daily was started. Steroid was tapered to 0.5 mg/kg daily in 1 year. At the end of this period the patient was in remission, but cataract and cushingoid appearance developed. Infliximab was started along with azathioprine to maintain her in remission, and prednisolone was tapered to 0.25 mg/kg daily. At the end of the first year of infliximab treatment MR angiography revealed regression of all the arterial stenoses (right renal artery, superficial femoral arteries, and carotid arteries) except for totally occluded superior mesenteric artery (Figure 2). She was in remission with no new lesion at the 42-month followup.

All patients with hypertension received antihypertensive drugs and 10 patients underwent surgical treatment. The main indication for intervention was renal vascular hypertension. Fourteen of the 17 hypertensive patients had renal artery stenosis (25 units) and 10 underwent surgery or interventional therapy (Table 5). The most common procedure was percutaneous transluminal angioplasty (PTA), which was performed in 4 patients (8 units). Two required stents because of reocclusion, which developed immediately after PTA. Aorto-renal bypass graft was performed in 3 patients (5 units) with renal artery stenosis, and all survived. Unilateral nephrectomy was performed in 2 hypertensive patients (2 units). One of these patients was admitted with severe hypertension and atrophic kidney, and unilateral nephrectomy was carried out. However, after 6 months she was diagnosed with TA because of recurrence of renal artery stenosis on the contralateral side. The other patient had severe hypertension, with bilateral renal artery involvement, and the removed kidney was atrophic. A thoraco-abdominal aortic bypass graft was performed in 2 patients who had stenosis of abdominal aorta. Renal autotransplantation was performed in 1 patient (1 unit).

DISCUSSION

TA has a worldwide distribution, although the disease is most common in Asia. Different patterns of clinical, demographic, and angiographic features of the disease have been described in various ethnic populations, with very few reports about childhood TA.



A B

Figure 2. Angiograms of the patient treated with infliximab. A. MR angiogram shows an irregularity and stenosis (arrow) in proximal part of the right renal artery and mild oststenotic dilatation. B. Followup examination after 2 years revealed normal right renal artery. Left renal artery is not visible.

Onset of TA is most common during the third decade of life. Park, *et al* reported that in a series of 108 Korean patients with TA, only 7 (7%) were under 10 years of age, and 21 patients (19%) were 10–20 years old at onset of disease[5]. In an Italian nationwide study, only 15% of the 104 patients were under age 15 years at onset[3]. Stanley, *et al* reported from Los Angeles that 23 children (age range 7 months to 14 years) were seen at their institution during 30 years[7]. The mean age of our patients was 12.84 years, which was higher than in other reports[6,7,17], with a female:male ratio of 2.8:1, similar to the significant preponderance of female children with TA reported previously[4-7,17].

Delay in diagnosis ranged from 1 to 60 months (median 12 months). Although this is shorter than in previous adult and pediatric series[3,8], it is still a lengthy period for the diagnosis. We suggest that there are several causes for this delay. One is that nonspecific constitutional symptoms such as weakness, fatigue, weight loss, and fever were known to be the most common presenting features of the disease[8]. In our series nearly 60% of patients had constitutional symptoms at presentation. Fever and abdominal pain were seen in more than one-quarter and one-third of them, respectively. Moreover, headache was present in more that 80% of the patients and 37% had dizziness. These results suggest that clinicians should consider these nonspecific symptoms as important for early diagnosis. The frequency of neurological manifestations in TA was reported to be between 42% and 57%[18,19], and it rose to 90% if headache and dizziness were included, and these were suggested to result mainly from decreased blood flow, hypertension, and thromboembolism[20]. Hypertension was the most common presenting feature, seen in 90% of our patients, and most had renal artery stenosis. Similar findings have been reported by others[4,6,7,17]. All patients with dizziness and 14 out of 16 patients with headache had hypertension, and 2 patients with dizziness and 9 with headache had carotid or vertebral artery involvement. Moreover, serious visual loss in one patient was found to be significantly correlated with ischemia caused by involvement of the carotid and vertebral arteries. Thus, TA should be considered in the differential diagnosis of every child who has hypertension and nonspecific clinical and/or neurological manifestations.

Ten of our patients were diagnosed and treated for other diseases before the diagnosis of TA. Two were diagnosed as seronegative spondyloarthropathy. Patients' history and clinical courses led us to believe that the 2 diseases had simultaneous onset. The occurrence of the 2 diseases is well known and this might result in a delay in diagnosis of TA, especially because most of the patients had arthritis and/or arthralgia.

Definite diagnosis of TA in the acute phase is difficult. Conventional angiography is usually mandatory in the initial evaluation of the disease. However, in recent years noninvasive imaging procedures such as CT and MR angiography have proven to be useful[10-12]. Although the luminal changes are well depicted with conventional angiography, mural

Table 5. Outcomes of patients who underwent surgery or interventional therapies.

Patient's Age (yrs) and Sex	Followup Period, mo	First Angiographic Findings	Interventions/Surgery	Last Angiographic Findings
11 F	168	Occlusion and aneurysms of SA and brachial arteries, occlusion of right CA, narrowing of right VA and abdominal aorta, stenosis of celiac truncus, SMA, and RA bilaterally	Autotransplantation of left kidney	Function and blood supply of left kidney normal. Other findings same as first angiography
12 M	90	Fusiform dilatation of arcus, thoracic and descending aorta, occlusion of left RA	Nephrectomy left kidney	Narrowing of SMA and celiac truncus
14 F	42	Occlusion of right CA, SMA, superficial femoral arteries; narrowing of right RA	Nephrectomy left kidney	Recanalization of occluded and narrowed arteries, except SMA
15 F	33	Narrowing of descending and abdominal aorta and right RA	Balloon angioplasty right RA. One year later balloon angioplasty to aorta and left RA	Narrowing of thoraco-abdominal aorta, ostium of celiac truncus, and left RA
15 F	30	Occlusion of origin of left CA and left SA, narrowing of proximal abdominal aorta and celiac truncus	Thoraco-abdominal aortic bypass	New narrowing and vessel-wall thickening of distal part of aortic bypass
16 F	24	Narrowing of CA bilaterally, descending and proximal part of abdominal aorta. Occlusion of right RA, narrowing and poststenotic dilatation of left RA, narrowing of SMA	Bilateral aorto-renal bypass	No new lesion
14 F	9	Wall thickening of CA bilaterally, thoracic aorta, abdominal aorta, narrowing of SA bilaterally, RA bilaterally	Stent to left RA	—
17 F	6	Diffuse thickening of descending aorta, pulmonary arteries, SMA, narrowing of proximal part of abdominal aorta ostium of RA bilaterally	Thoraco-abdominal aortic and bilateral aorto-renal bypass	—
15 M	2	Occlusion of right RA, narrowing and poststenotic dilatation of left RA	Aorto-renal bypass graft and balloon angioplasty to right RA, balloon angioplasty to left RA	—
12 F	2	Narrowing of right SA, right and left CA; occlusion of left SA and narrowing of RA bilaterally	Balloon angioplasty and stent to right RA and left RA	—

CA: carotid artery, SA: subclavian artery, RA: renal artery, SMA: superior mesenteric artery, VA: vertebral artery.

changes are best evaluated with CT or MR angiography. MR angiography may be particularly useful in detection of early signs of large-vessel disease, and it has the added advantage of revealing evidence of ongoing vessel-wall inflammation[10,11]. Laboratory markers may be entirely normal despite ongoing inflammation[18]. Our results also suggest that MR angiography provides additional information about the presence of vascular inflammation and/or wall thickening compared to conventional angiography, and it is very useful for serial evaluation of patients undergoing treatment.

There have been several classifications of the distribution of angiographic abnormalities seen in TA. In our series abdominal aorta was involved in 17 of the 19 patients, and 12 had involvement of the aortic arch and its major branches. These forms of arterial involvement have also been more frequent in other series[4,6]. Pulmonary arteritis is an important feature of TA that is not found in other forms of vasculitis; its frequency has been reported to be as high as 50%–80% in some series[7,21]. We suggest that failure to perform routine pulmonary angiography in all our patients resulted in underestimation of its frequency in our series.

In our patients, stenosis occurred more frequently than other lesions in TA[3,7,8]. In the National Institutes of Health study, the most commonly involved vessels were reported as the innominate and subclavian arteries (93% of cases), aorta (65%), common carotid arteries (58%), and renal arteries (38%)[8]. In our series stenosis or occlusion of renal artery was the most common, followed by subclavian and carotid artery stenosis and occlusions. Symptoms of limb hypoperfusion were seen in only 6 of the 19 patients because of the collateral circulation.

As with all vasculitides, early diagnosis and prompt therapy are important in TA to prevent irreversible vessel damage with resulting compromise of vital organs. Corticosteroids are still the mainstay of treatment. In addition, MTX, azathioprine, mycophenolate mofetil, and cyclophosphamide have been used in treatment of TA[9,13]. Most authors recommend cyclophosphamide only for patients with severe TA refractory to other immunosuppressive drugs. Ozen, *et al* described 6 children with TA, and treatment with steroid and cyclophosphamide induction followed by MTX was suggested as effective and safe for childhood TA with widespread disease[22]. However, there are no evidence-based data about a single agent better than any

other for the treatment of TA. Anti-TNF therapy might be beneficial in TA, and a high rate of response to TNF inhibitors has been reported[23,24]. In our series, infliximab was used in only 1 patient, and in this case occluded vessels were recanalized. Before starting such a treatment, it is important to test patients for tuberculosis.

Besides medical therapy, surgical intervention is frequently required to alleviate end-organ ischemia resulting from vascular damage[6,25,26]. In our series PTA was performed in 8 of the 21 instances of stenotic renal arteries, PTA with renal artery stent in 2, aorto-renal bypass graft in 5 renal arteries, and thoraco-abdominal bypass in 2 patients. Renal autotransplantation was performed in one patient and the kidney survived for 14 years. None of the stenoses of subclavian and carotid arteries needed revascularization because of adequate collateral circulation. These results show that surgery should be reserved for patients with cerebrovascular and limb symptoms due to ischemia.

TA is an inflammatory arteritis found predominantly in female patients. Hypertension is the most common clinical feature at presentation. Better awareness among pediatricians of the diagnosis of TA is necessary in our country. It can occur in children with characteristic angiographic features. MR angiography could be recommended as the primary investigation method in children with TA. Corticosteroid and immunosuppressive therapy were effective in control of disease activity. Although angioplasty or bypass grafting is feasible, only longterm followup can determine whether these therapies can be equally recommended.

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