

Clinical characteristics, interdisciplinary treatment and follow-up of 14 children with Takayasu arteritis

Wei-Hua Zhu, Lai-Gen Shen, Henning Neubauer

Hangzhou, China

Background: Pediatric patients with Takayasu arteritis were studied by analyzing clinical presentation, diagnostic images, response to multimodal therapy, and long-term outcome.

Methods: Fourteen consecutive children and adolescents (mean age: 10 years) were diagnosed with Takayasu arteritis at our institution between 1995 and 2007. They were subjected to clinical and diagnostic studies including color ultrasonography, MRI and angiography, and received interdisciplinary treatment.

Results: The median time lag between the first onset of symptoms and diagnosis was 7.7 weeks. The majority of patients presented with acute severe clinical symptoms and extensive vascular lesions. Hypertension was the most common finding on first presentation (93%), followed by headache (64%), nausea (64%) and palpitation (50%). Ten patients (71%) had reduced or absent carotid, brachial or femoral pulses in one or more locations. C-reactive protein was elevated in 79% of the patients and erythrocyte sedimentation rate in 64%. Cardiovascular imaging showed extensive vasculitis of both sides of the diaphragm in 86%. Complications included renal artery stenosis ($n=7$), aortic dissection, thoracic aortic aneurysm and infrarenal aneurysm (all $n=1$). Conservative drug treatment was effective in 50%. Interventional dilatation of stenosis and surgical therapy, including aortic bypass, resection of aneurysms and nephrectomy, were necessary in the remaining patients. Follow-up for 25 months to 12 years showed that all children are well without disease-related

mortality.

Conclusions: Takayasu arteritis is a rare and potentially life-threatening disease in children, likely with a prolonged subclinical course. Rapid diagnosis and interdisciplinary management help to prevent life-threatening complications.

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Key words: children; complications; diagnosis; Takayasu arteritis; therapy

Introduction

Takayasu arteritis (TA) is a rare condition predominantly affecting young individuals across geographic regions and ethnicities.^[1] In spite of the generally low incidence in children, TA is ranked among the more common causes of vasculitis in pediatric patients.^[2] Descriptive diagnostic criteria of varying sensitivity and specificity have been proposed^[3-5] and a new classification for TA in pediatric patients has been introduced.^[6] However, the etiopathogenetic background of what is histologically seen as a fibrosing panarteritis affecting the aorta and the large and middle-sized arterial branches remains widely unclear. Associations with certain human leukocyte antigen subtypes,^[7] abnormal T lymphocyte function^[8] and tuberculosis^[9] have been reported; however, the clinical significance of these findings is uncertain. Differences in clinical characteristics between ethnic groups, both in adults and children, regarding the regional distribution of arterial wall lesions, clinical symptoms and complications have been documented.^[10-17]

Controversy focuses on whether pediatric patients show characteristic clinical manifestations other than those encountered in adult populations.^[11,12] To date, there is only a single report on TA patients of Chinese ethnicity in the literature, presenting data from a mixed group of 530 cases, including children, adolescents and adults.^[18] We studied a group of Chinese school children with TA, analysing clinical characteristics, modes of

Author Affiliations: Department of Cardiology, Children's Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China (Zhu WH); Department of General Surgery, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou 310016, China (Shen LG); Institute of Radiology, Department of Paediatric Radiology, University Hospital Wuerzburg, 97080 Wuerzburg, Germany (Neubauer H)

Corresponding Author: Henning Neubauer, Helmuth-Zimmerer-Strasse 71, 97076 Wuerzburg, Germany (Tel: 0049-931-201-34715; Fax: 0049-931-201-34857; Email: henning_neubauer@web.de)

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treatment, as well as complications and outcome.

Methods

Between August 1995 and January 2007, we collected data on a total of 14 consecutive patients with TA aged 16 or younger who were admitted to Children's Hospital, Zhejiang University School of Medicine. All patients were diagnosed by one experienced pediatric cardiologist according to the criteria issued by the American College of Rheumatology and the EULAR/Pres classification.^[4,6]

A detailed clinical history was obtained and a comprehensive physical examination was performed in all children, including the elaborate pulse status of all accessible arterial vessels and blood pressure measurement in all four limbs with pediatric cuffs according to a standardized procedure (supine position after at least 5 minutes resting). Routine assessment included ophthalmological examination, chest X-ray, echocardiography (13 patients), thoracic and abdominal B-mode ultrasonography and Doppler ultrasonography of the central arterial vessels. All patients underwent aortography and selective large vessel angiography to assess the vascular status and to chart the regional distribution of arterial wall lesions. Eight patients were additionally examined with MR-angiography. All patients received treatment and were followed up at our institution annually, including clinical and laboratory examinations as well as vascular ultrasound. Follow-up after interventional or surgical treatment was scheduled at one month, 3 months and 6 months intervals after intervention, including vascular assessment with ultrasound, computed tomography, angiography or magnetic resonance angiography when necessary. Response to treatment was considered successful if signs or symptoms of the disease were absent, laboratory results were normal, and new vascular abnormalities were not identified. Remission was considered if these criteria were met and the patient required less than 10 mg prednisone per day.

Data were analysed and presented as numbers of cases and percentages. The Microsoft Office 2007 software package was used for data extraction and correlation analysis.

Results

Clinical and laboratory findings

In this series, 11 were girls and 3 boys (gender ratio 3.7:1), all of Chinese Han ethnicity, with a mean age of 10.2 years (range 7-16 years, median 10 years) at first admission. All children were normally developed with a body mass index within the age-specific reference

ranges. None of them had a family history of vasculitis. The median time lag between the onset of symptoms and the first referral to our hospital was only 4 weeks (range from 1 week to 1 year). Nine patients (64%) came to the hospital within one month after the first symptoms had occurred. The time interval between the first hospital admission and diagnosis of TA ranged from 1 to 415 days, with an average of 53 days and a median of 19 days. The median time lag between the reported onset of symptoms and diagnosis was 7.7 weeks. The patients were followed up between 25 months and 12 years with a median of 60 months.

Headache (64%) and nausea (64%) were the most commonly encountered initial manifestations followed by palpitation (50%) and arthralgia in one or more joints (43%). Fever (29%) and visual complaints (21%) were less common (Table 1). Clinical evaluation revealed hypertension as the cardinal finding in 93%

Table 1. Symptoms on the first hospital admission

Symptoms	Cases (%)
Headache	9 (64)
Nausea and vomiting	9 (64)
Palpitations	7 (50)
Arthralgia	6 (43)
Weight loss	5 (36)
Ischemia/ Claudication	4 (29)
Fever	4 (29)
Visual complaints	3 (21)
Dyspnea	3 (21)
Chest pain	3 (21)
Syncope	2 (14)
Stroke	0 (0)

Table 2. Clinical findings on the first hospital admission

Symptoms	Cases (%)
Hypertension	13 (93)
Mean blood pressure, SBP/DBP, mmHg, <i>n</i>	
Right arm	165/104
Left arm	145/86
Right leg	152/101
Left leg	143/103
Pulse status, normal/reduced/no, <i>n</i>	
Carotids	12/2/0
Upper limbs	11/2/1
Lower limbs	8/5/1
Cardiac murmur	5 (36)
Congestive heart failure	4 (29)
Bruit – subclavian artery	3 (21)
Bruit – abdominal aorta	3 (21)
Ophthalmopathy	3 (21)
Seizures	3 (21)
Hypertensive encephalopathy	2 (14)
Pleural effusion	1 (7)
Pericardial effusion	1 (7)
Carpopedal cramps	1 (7)
Cardiomyopathy	1 (7)
Paresis	1 (7)

SBP: systolic blood pressure; DBP: diastolic blood pressure.

and reduced or not palpable pulses in the carotid, subclavian and femoral arteries in 14%, 21% and 43% of the patients (Table 2). One patient with reduced carotid pulses and non-palpable femoral pulses showed slight paresis of the lower limbs, right 4/5 and left 3/5, in the neurological status. Cardiac murmurs were found in 5 patients on auscultation; echocardiography revealed significant aortic valve regurgitation and left ventricular hypertrophy in 3 patients. Bruits in the subclavian artery were found in 3 patients (21%) with correspondingly reduced (2 patients, left subclavian artery) or not palpable (one patient, right subclavian artery) pulses and angiographically verified stenoses. Three patients with abdominal bruit also had reduced femoral pulses and significant stenoses in the abdominal aorta.

Laboratory results were positive for markers of inflammatory disease and for anemia in the majority of patients (Table 3). Elevated ESR showed an inverse, but non-significant correlation with hemoglobin ($r=-0.45$, $P=0.14$, Pearson's correlation coefficient) and hematocrit ($r=-0.56$, $P=0.06$). In spite of a positive Mendel-Mantoux test in 3 patients (21%), none of the participants showed signs of acute tuberculosis. ESR and CRP were not correlated significantly with the extent of vascular involvement, nor with the duration of symptoms before the first hospital admission or with the time lag between hospital admission and diagnosis.

Diagnostic imaging

B-mode ultrasound revealed thickening and signal increase of the vascular wall as well as a varying degree of vascular stenosis. Color-doppler ultrasound showed aliasing and turbulent flow in the descending and abdominal aorta with peak velocities of up to 2.5 m/s.

Angiography demonstrated TA type IIb in 2 patients (14%), type III in 7 (50%), and type V in 5 (36%), according to the classification proposed by Moriwaki et al,^[19] which were confirmed by MR angiography in all 8 patients examined. Thoracic and abdominal aorta showed circumscribed stenoses between 0.5 cm and 3 cm of length with adjacent irregularities of the vascular wall as characteristic lesions. Ectatic lumina was seen in 3 patients. The carotid arteries were bilaterally involved

in 2 patients, and the subclavian arteries in 4 patients (left subclavian artery only in 2 patients and another 2 patients with bilateral lesions). Bilateral renal artery lesions were seen in 5 patients, including 3 patients with right kidney hypotrophy, and left renal artery lesions in another 2 patients including one with an atrophic left kidney. Superior mesenteric artery involvement was diagnosed in one patient. Pathological alterations were not observed in the pulmonary and the coronary arteries.

Follow-up showed that dissection of the thoracic and abdominal aorta extended from TH4 to L2 in a 16-year-old girl on follow-up. Retrograde transfemoral catheterization of the femoral artery depicted the false lumen with a retrograde flow; transbrachial catheterization demonstrated the true lumen with a largely reduced antegrade flow and the pathological alterations of the vascular wall (Fig. 1).

One patient had a saccular aneurysm of the descending thoracic aorta, measuring 1.5 cm in diameter (Fig. 2). Another patient was diagnosed with



Fig. 1. Dissection of the thoracic and abdominal aorta in a 16-year-old girl with Takayasu arteritis.

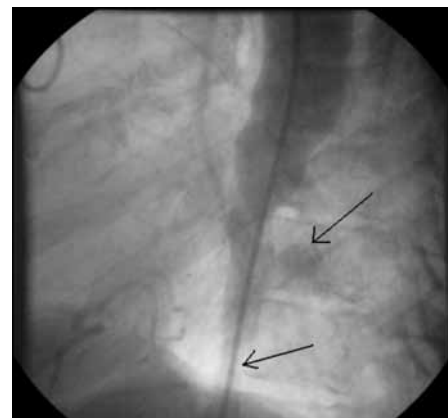


Fig. 2. Formation of a saccular aneurysm with 1.5 cm in diameter in the descending aorta (upper arrow) and stenotizing aortitis (lower arrow) in a 16-year-old girl with Takayasu arteritis.

Table 3. Laboratory findings

Variables	Cases (%)
CRP >8 $\mu\text{g/L}$	11 (79)
Hemoglobin <10 g/dL	10 (71)
ESR >20 mm/1 h	9 (64)
Mendel-Mantoux >10 mm	3 (21)
Hematuria	2 (14)
Serum creatinine >2 mg/dL	1 (7)

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

an aneurysm of 4.5 cm in diameter in the infrarenal aorta. This patient also had stenotic renal arteries and suffered from therapy-resistant hypertension.

Therapy and outcome

Anti-inflammatory treatment was initiated with oral doses of non-steroid anti-inflammatory drugs (NSAIDs) or glucocorticoids (prednisone 0.5-1 mg/kg per day orally) as symptomatic treatment. In the course of treatment, steroid doses were kept to the lowest therapeutic level aiming at normal levels of CRP, ESR and leukocyte. Low-dose aspirin (3-5 mg/kg per day) was administered for anticoagulation therapy. Captopril (1.5-3 mg/kg per day tid, maximum dosage 12.5 mg tid) or enalapril (0.05-0.1 mg/kg per day, maximum dosage 1 mg/d) was given for anti-hypertensive treatment, with addition of hydrochlorothiazide, spironolactone, nifedipine or propranolol if necessary. Purified protein derivative positive children were treated with oral doses of isoniazid for 6 to 12 months. Anti-hypertensive treatment could effectively control blood pressure in 7 patients (50%). In some of these patients, temporary administration of increased doses of antihypertensives was necessary to keep blood pressure within the normal range.

Anti-hypertensive treatment was ineffective in 7 patients. In three of them, stenotic sections of the descending aorta were treated with percutaneous transluminal angioplasty. Post-interventional blood pressure measurements showed a certain relief and remained within or near the normal range with a low-dose of oral captopril. In one patient, however, undulating hypertensive pressures were seen on follow-up, and two years after intervention blood pressure returned to the pre-interventional level.

Five patients underwent surgical treatment. Bypass grafting from the ascending aorta to the abdominal aorta was performed in two patients. A Goretex vascular prosthesis with a diameter of 16 mm and a length of 30 cm was implanted in the two patients, inserting 3 cm cranially from the thickened section in the thoracic aorta, crossing the diaphragm and connecting with an end-to-side anastomosis to the left common iliac artery. In the third patient, a descending aorta bypass was combined with a superior mesenteric artery bypass and right-sided nephrectomy. Two patients were treated with unilateral nephrectomy. All of the 5 surgically treated patients recovered well. Postoperatively, the difference of their blood pressure between the upper and lower extremities was no longer present. The blood pressure returned to normal with a remaining undulating pattern, so that anti-hypertensive treatment was maintained for two weeks after operation. At that time, blood pressures normalized and administration of antihypertensive

medication was no longer necessary. Postoperative anticoagulation was maintained for 1 to 3 months, and PPT and prothrombin time were measured every 2 weeks.

Follow-up for 12 years (median 36 months, 9 patients >3 years) showed all of the patients are well without life-threatening complications.

Relapse in terms of recurrent laboratory signs of inflammation was observed in 2 patients, who required long-term anti-inflammatory medication. Hypertension normalized in 12 patients after 6 months to 3 years of anti-hypertensive treatment, while 2 patients showed persistent hypertension with the necessity of continuing drug treatment without serious side-effects. Extension of vascular involvement was not found during the follow-up.

Discussion

TA is considered as idiopathic vasculitis and has a low incidence in pediatric populations. Data from large patient cohorts are not available, and therefore there are no evidence-based guidelines for treatment of children with TA. In this study we analyzed the data of 14 patients treated in a period of 12 years. The male/female ratio was 1:3.7, which is comparable to that of 1:4.4 in Korean children^[15] and 1:2.9 reported from a large sample of Chinese patients.^[18] Studies from India reported a male/female ratio between 1:1.1^[11] and 1:5^[12] in children and adolescents.

Hypertension is the most common finding on admission, which is similar to the finding in Korean, Mexican, Turkish and French children.^[10,14,15,20] All but one child in our study showed elevated systolic and diastolic blood pressures beyond the normal range, as previously observed in other cohorts.^[20] Admitted to our hospital were 2 children with hypertensive crisis in excess of 200/120 mmHg. A blood pressure difference of 20 mmHg or more was observed between the upper and lower extremities in 50% of the patients.

A remarkable feature of our study cohort is the short average time lag between the reported onset of symptoms, first hospital admission and definite diagnosis of TA. In most patients, the diagnosis of TA was established soon after the first outpatient visit, once arterial wall lesions had been suspected on vascular ultrasonography. Diagnostic angiography confirmed the diagnosis within 2 months or less from the onset of symptoms in 57% and within four months in 79% of the patients. Previous studies reported a delay of 4 months between initial symptoms and the first hospital admission and of 2 years until the definite diagnosis.^[12,21]

Still there was a discrepancy between the acute onset of symptoms and the extensive vascular lesions observed in the majority of our patients.

One may assume that a prolonged subclinical period preceding the onset of acute disease is necessary for morphological changes of the large vessels. According to the angiographic criteria proposed by Moriwaki et al,^[19] we found extensive vascular involvement on both sides of the diaphragm (type III: descending thoracic aorta, abdominal aorta and/or renal arteries in 50%; type V: generalised type in 36%) in 86% of our patients. This involvement is consistent with the finding in Turkish and Indian children.^[10,12] Lesions limited to the descending thoracic aorta with or without involvement of the thoracic aorta and the supraaortal vessels (type IIb) were seen in 14% of the patients only. As reported elsewhere,^[12,22] Type I (isolated disease of the supraaortal branches) was not observed in our study. We also did not find vascular lesions confined to the abdominal aorta, or pulmonary/coronary artery lesions.

A peculiar finding in our study is the relatively high percentage of patients with symptoms of acute systemic inflammation (elevated CRP in 79% of the patients, ESR in 64% and fever in 29%). In previous studies from India, febrile temperatures were only found in 17.6%, and 4% of the children, elevated CRP in 17.6% and ESR in 65% and 42%, respectively.^[11,12] Hypertension combined with elevated ESR was reported as a diagnostic feature of comparably high sensitivity in children.^[23]

In our study one patient with aortic dissection involving the thoracic and abdominal aorta and two patients with aneurysms were all discovered by follow-up angiography. Aortic aneurysm and aortic dissection are rarely seen in children. To date there is only one reported case of aortic dissection secondary to TA in a 9-year-old girl.^[24] Our data showed that Takayasu's arteritis seems to have a certain risk of aneurysmatic dilatation and dissection of the aortic vascular wall that follow-up examinations of children with TA should not fail to address. As early diagnosis and timely treatment may help to prevent or to manage these complications, hypertensive children with a blood pressure difference between the upper and lower limbs and signs of systemic inflammation deserve particular attention, including early referral to cardiovascular imaging, i.e., cardiovascular ultrasound, MR angiography and/or conventional angiography.^[25] In our study, symptomatic anti-inflammatory, antibiotic and anti-hypertensive drug treatment was suitable and sufficient for one half of the children. Hypertension was not satisfactorily controlled with conservative treatment in the remaining children. Immunosuppressive treatment was not prescribed with methotrexate, azathioprine, cyclophosphamide or anti-TNF α -drugs as proposed for severe refractory TA.^[26,27] Percutaneous transluminal angioplasty performed in 3 children with stenoses of the descending aorta was only

partially beneficial for a certain relief of hypertension as reported.^[11] One of these children was treated surgically 7 years after the initial percutaneous transluminal angioplasty. Stent implantation is a feasible option for adults, but not children,^[28] as the implanted material cannot adapt to the growing organism. For surgical treatment, aortic stenoses are bridged with a Goretex bypass. In addition, aortic aneurysm and nephrectomy in patients with renal atrophy could be resected. The growth of young patients needs to be considered when planning the bypass graft, and from the surgical point of view conservative treatment should be maintained until the end of the pubertal growth period. From our experience, surgical treatment is indicated for patients with aortic or branch vessel stenosis of more than 70%, impaired blood-supply to the visceral organs, complications such as aortic aneurysm and dissection, and insufficiency of the aortic valve leading to impaired cardiac function and therapy-resistant hypertension. Surgical intervention in our study led to satisfactory long-term results including a low morbidity and no peri-operative or post-operative deaths.^[28]

Coronary and pulmonary artery involvement has been reported in TA patients.^[29] Although invasive diagnostic procedures, i.e., cardiac catheterization or thoracic CT angiography were not performed to identify vascular lesions in these locations, none of our patients showed clinical signs of pulmonary artery involvement or myocardial ischemia secondary to coronary artery occlusion.

TA continues to pose a diagnostic and therapeutic challenge, particularly in young patients, for general practitioners as well as cardiovascular specialists. Careful clinical assessment and routine diagnostic imaging with vascular ultrasonography and MRI are necessary in children with hypertension, unspecific signs of systemic inflammation and suspected vascular involvement. Early diagnosis facilitates adequate treatment and may help to prevent life-threatening complications. Interdisciplinary cooperation in diagnosis and treatment can apparently achieve a satisfactory outcome in most pediatric patients with a low mortality and morbidity. Observations based on larger patient samples are desirable, but may not be available in the near future due to the comparably low incidence of TA in young patients.

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Contributors: Zhu WH is the initiator and guarantor of the study and responsible for study design, data acquisition, as well as patients' treatment. Shen LG participated in study design, literature review and manuscript drafting and revising. Neubauer H was

primarily responsible for literature review, data processing, and statistical analysis.

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