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Retrospective Clinical Study of Patients with Takayasu's Arteritis

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ABSTRACT

Objective: To study the clinical features angiographic findings, treatment response and prognosis of patients with Takayasu arteritis.

Methods: Seventy-three patients with Takayasu arteritis admitted into our hospital between January 2006 and August 2011 were evaluated retrospectively for the clinical manifestations, laboratory testings, angiographic findings, treatment response and prognosis of the disease.

Results: There were twenty male cases, 53 female cases of 73 patients with Takayasu arteritis, the ratio of male to female was 1:3.8. The mean age of onset was (33.9±12.0) years old (yo), and the median age at onset of first symptoms of the disease was 26 yo (range 14-63 yo). Five patients of them were less than 18 yo, and 22 patients were over 40 yo. The incidences of dizziness, malaise, hypertension, acrotism or pulseless, vascular bruits and asymmetric blood pressure were present separatively in 60%, 40%, 70%, 30%, 72% and 54%. Angiographic findings showed that Type Ⅰ (36%), Type Ⅳ(23%), Type Ⅴ(25%) were common, and Type Ⅱa (1%), Type Ⅱb (7%), Type Ⅲ (8%) were seldom seen. Disease activity of Takayasu arteritis should be evaluated according to level of elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which were present in 33% and 37% of patients, respectively. Fifty-eight patients underwent different angiographies, 29 of them accepted the stenting implantation. Ten interventions (34.5%) restenosed (31.4±11.7%) months after intervention. Seventy patients (96%) received Aspirin (100mg/d) therapy, three patients (4%) received clopidogrel at a daily dose 75mg, twenty-four of them received glucocorticoids with immunosuppressive agents and 14 patients received glucocorticoids alone. Of patients with intervention, non-intervention and restenosis, there was no difference in mean age (P=0.25), ESR (P=0.47) and CRP (P=0.98); whereas, there was statistically significant difference in mean age (P=0.007), ESR (P=0.044) and CRP (P=0.001), among patients with glucocorticoids and immunosuppressive agents, none of them and alone.

Conclusions: Clinical signs and symptoms of patients with Takayasu arteritis (TA) were atypical in the early stage. Physicians should increase awareness to prevent delay diagnosis in TA. Angiography was the gold standard for diagnosis. Sedimentation rate (ESR) and C-reactive protein (CRP) contributed to guide the treatment of patients with TA and evaluate the disease activity.

INTRODUCTION

Takayasu arteritis (TA) is a chronic non-specific inflammatory disease that affects large vessels, mainly the aorta and its primary branches, including the coronary, carotid, pulmonary and renal arteries. It is also called pulseless disease.[1-3] Vessel inflammation and subsequent intimal proliferation of the arterial wall may lead to lumen stenosis and occlusion, while aneurysms may result from an inflammatory process involving the elastic lamina of the arteries.[1-2] TA was once presumed to be a disorder that mostly affected young Asian women[4]. Next, TA has been identified in both sexes and many ethnic and racial groups worldwide. The incidence of TA has been reported to be 2.6 cases per million per year in Olmsted County, Minnesota[5]. Due to low incidence, knowledge about the clinical course and therapeutic approaches in TA remains exclusively based on case series from different countries. So, in this study, we retrospectively evaluated the clinical manifestations, laboratory testings, angiographic findings, treatment response and prognosis of 73 patients with TA from our hospital.

PATIENTS AND METHODS

73 patients with Takayasu arteritis were admitted into General Hospital of the People's Liberation Army from January 2006 to August 2011. There were twenty males and fifty-three females with ages ranging from 14 to 63 years at the onset. All patients had complete clinical data, including personal information, angiographic and laboratory findings, diagnosis and treatment.

CLINICAL FEATURES AND LABORATORY FINDINGS

Takayasu arteritis (TA) had no typically clinical characteristics in the early stage. Clinical features range from asymptomatic disease to catastrophic neurological impairment. Non-specific features including fever, night sweats, malaise, dyspnea and anemia[5]. If patients with TA have specific features, including hypertension, pulse deficit, vascular bruits and limb claudication, which show that limb or organ, ischemia results from vessel inflammation leading to vessel wall thickening, fibrosis, stenosis, and thrombus formation. There is no specific inflammatory marker to diagnose TA. Disease activity of Takayasu arteritis should be evaluated mainly according to level of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). However, these indicators lack sensitivity and specificity[6].

DIAGNOSTIC CRITERIA AND CLINICAL CLASSIFICATION

All patients were diagnosed according to the 1990 American College of Rheumatology (ACR) criteria [7] **(Table1)**. Disease activity was evaluated according to the National Institutes of Health criteria for active disease [2]. These criteria included constitutional symptoms, such as fever and musculoskeletal symptoms, elevated ESR, features of vascular ischemia or inflammation, such as claudication, diminished or absent pulse, bruit, vascular pain, blood pressure difference in the upper or lower extremities, and typical angiographic findings. New onset or worsening of two or more features defined active disease and a decrease in symptoms and signs or complete resolution of clinical features was indicative of stable disease. In the present study, Takayasu arteritis was classified into six types and a new classification was based on angiographic findings[8]: Type I: Branches of the aortic arch; Type IIa: Ascending aorta, aortic arch and its branches; Type IIb: IIa lesions+thoracic descending aorta; Type III: Thoracic descending aorta, abdominal aorta, and renal arteries; Type IV: Abdominal aorta and/or renal arteries; Type V: Type IIb+IV (ascending aorta, aortic arch and its branches, and thoracic descending aorta as well as abdominal aorta and/or renal arteries). A comparison of affected lesions showed that the incidence of Type Ⅰ (36%), Type Ⅳ(23%), Type Ⅴ (25%) was higher, whereas the incidence of Type Ⅱa (1%), Type Ⅱb (7%),Type Ⅲ (8%) was lower.

Table 1. 1990 ACR criteria for the classification of Takayasu arteritis

Criterion	Definition
Age at disease onset <40 years	Development of symptoms or findings related to Takayasu arteritis at age <40 years
Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of 1 or more extremity while in use, especially the upper extremities
Decreased brachial artery pulse	Decreased pulsation of 1 or both brachial arteries
Blood pressure difference >10mmHg	Difference of >10 mm Hg in systolic blood pressure between arms
Bruit over subclavian arteries or aorta	Bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta
Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not caused by arteriosclerosis, fibro muscular dysplasia, or similar causes; changes usually focal or segmental

＊A diagnosis of Takayasu arteritis requires that at least 3 of the 6 criteria are met.

MEDICAL TREATMENT

Previous studies[9] show that the use of corticosteroids is thought of first-line medical treatment for Takayasu arteritis (TA) as anti-inflammatory agents. Adjunctive antiplatelet or anti-hypertensive agents are recommended as second-line medical treatment in patients with TA. Evidence signifies that long term corticosteroid therapy contributes to improvement of angiographic features[10-11]. Initial therapy for active disease generally consisted of corticosteroid only (1 mg/kg/day) for 3 months, which was then tapered at a rate of 5 mg every 2 weeks down to 10 mg and thereafter at a rate of 2.5 mg every 2 weeks until withdrawal or to the minimum required dose to control inflammation, while the erythrocyte sedimentation rate and serum C-reactive protein concentration are monitored. Immunosuppressive drugs are used only as a supplementary therapy because of their adverse effects and resistance to drugs.

STATISTICAL ANALYSIS

Numerical data were presented as means plus or minus the standard deviation (mean +/- SD). Categorical data were presented as total number and percentage of cases. The comparison between two groups was performed with q-test. Statistical significance was evaluated by analysis of variance (ANOVA) using SPSS version 17.0.P values less than 0.05 were considered statistically significant.

RESULTS

Clinical Features

Table 2 shows that there were twenty males (27%) and fifty-three females (73%), the ratio of male to female being 1:3.8. Thirty percent (22 of 73) of patients were over 40 and five patients were less than 18 years old. The mean age of onset was (33.9±12.0) years, and the median age at onset of first symptoms of the disease was 26 years (range 14-63 years).

Table 2. Clinical signs and symptoms of 73 patients with Takayasu arteritis

Index	Number (n)	Incidence rate(%)
Sex		
Female	53	73
Male	20	27
Clinical feature		
Age(>40years)	22	30
Fever	8	11
Diziness	44	59
Arthralgia or myalgia	11	15
Night Sweats	2	3
Malaise	29	39
Hypertension	52	69
Acrotism or Pulseless	22	29
Asymmetric blood pressure	40	53
Vascular bruits	53	71
Claudication	3	4
TIA	1	1
Dyspnoea	4	5
Angina	5	7
Aortic regurgitation	20	27
Visual disturbance	7	9
Laboratory finding		
ESR(>20mm/h)	25	33
CRP(>1mg/dL)	27	37
Elevated white cell	8	11
Anemia(<110g/L)	8	11
Rheumatoid factor(RF)	0	0

The most common clinical features was vascular bruits(71%), which were present most over the carotid arteries (40%) and less common in the abdomen (18%) and subclavian (16%) and femoral (10%) regions. Twenty percent of patients had multiple bruits. The incidences of dizziness, malaise, acrotism or pulseless, asymmetric blood pressure and arthralgia or myalgia were present separatively in 59%, 39%, 29%, 53% and 15%. Eight patients (11%) suffered from fever, but night sweats (3%) , dyspnea (4%) and claudication (5%) were uncommon. The most

Common cardiac findings were mild aortic regurgitation, which were present in 20 patients (27%). Hypertension occurred in

52 patients (69%) during the course of their disease. Ischemic events were observed in six patients, including one patient (1%) with transient ischemic attack and five patients (7%) with angina. Visual disturbance occurred in 7 of 73 patients (9%).

LABORATORY FINDINGS

The routine laboratory testing's performed in all patients. Evaluation of disease activity remained based on the level of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). According to the NIH criteria for active disease, there were 42 patients in active phase and 31 patients in inactive phase. Serum elevated ESR (>20mg/L) and CRP (>1mg/dL) correlated with active disease status, the ratio was present in 33% and 37%, respectively. Eight patients (11%) suffered from elevated white cell and anemia (hemoglobin less than 110mg/L) and Rheumatoid factor (RF) testing for all patients was negative.

ANGIOGRAPHIC FINDINGS

Table 3 shows that seventy-nine percent of patients(58 of 73) underwent angiography. Among 58 of 73 patients, there were 96 sites of affected arteries, of these arteries, subclavian artery was most often.

Table 3. Vascular procedures among 73 patients with Takayasu arteritis.

Procedure	patients(n)	Number of lesions (n)	Incidence rate(n/73,%)
Affected arteries	58	96	132
Subclavian artery		29	40
Common carotid artery		12	16
Branchiocephalic artery		6	8
Bilateral renal artery		10	14
Unilateral renal artery		17	23
Left main		4	5
Left anterior descending		4	5
Right coronary artery		1	1
Abdominal aorta artery		8	11
Popliteal artery		1	1
Pumonary artery		1	1
Iliac artery		1	1
Axillary and brachial artery		1	1
Superior mesenteric artery		1	1
Surgical treatment	42	47	64
Intravascular stenting implantation		29	40
Unilateral nephrectomy		3	4
Renal autotransplantation		1	1
CABG		1	1
Balloon angiography		5	7
Bypass or blood vessel prosthesis		8	1

Involved (40%), followed the unilateral renal artery (23%); and the common carotid artery (16%). Among the patients, 11% had abdominal aortic lesion, and 14% had bilateral renal artery lesions, 8% had branchiocephalic artery lesions. And, coronary artery lesions involved LM (5%) , LAD(5%) and right coronary artery (1%). only one patient had artery lesions among these arteries,including popliteal artery (1%), pulmonary artery (1%), iliac artery (1%), axillary and brachial artery (1%) and superior mesenteric artery (1%). Among major complications, aortic regurgitation was observed in one-third of the patients in Japan. Hypertension was present in 69%, eye symptoms in 16.4%, brain ischemia in 14.9%, ischemic heart disease in 10.7%, and aneurysm in 5% of patients.

MEDICAL TREATMENT

In the present study, antiplatelet therapy was prescribed for all patients with Takayasu arteritis (TA) at disease onset; seventy of patients (96%) took aspirin at a daily dose 100 mg and three patients (4%) received clopidogrel at a daily dose 75 mg. de Souza's study[12] have demonstrated that antiplatelet threrapy with aspirin reduces the risk of acute ischemic events, in particular cerebrovascular and cardiovascular, in patients with TA.

Glucocorticoids and immunosuppressive agents are still used in the active phase of TA. Disease activity of TA was judged by the erythrocyte sedimentation rate and C-reactive protein concentration. **Table4** shows that twenty-four patients with TA required therapy with glucocorticoids and immunosuppressive agents and fourteen patients received glucocorticoids alone, however, neither glucocorticoids nor immunosuppressive agents was used for 35 patients. The mean age, ESR and CRP shows a significant difference among the groups ($p<0.05$). The use of glucocorticoids and immunosuppressive agents is more prone to young patients (27.9±10.3years) with the level of elevated ESR (23.5±17.8 mm/h) and CRP (1.42±1.33 mg/dL).

⁎ $p<0.05$ is statistically significant.

Table 4. Comparision of mean age, ESR, CRP of groups with and without glucocorticoids and immunosuppressive agents therapy

Type	Utility of glucocorticoids and immunosuppressive agents(n=24)	Utility of glucocorticoids alone(n=14)	Utility of neither glucocorticoids nor immunosuppressive agents(n=35)	p value
Mean age(years)	27.9±10.3	34.6±9.7	37.8±12.7	0.007 *
ESR(mm/h)	23.5±17.8	25.3±16.2	15.4±10.9	0.044 *
CRP(mg/dl)	1.42±1.33	1.58±0.94	0.46±0.33	0.001 *

VASCULAR INTERVENTION AND SURGICAL TREATMENT

For the 73 patients retrospective study, there were 42 patients with Takayasu arteritis (TA) undergone vascular intervention (40%) and surgical treatment (24%) **(Table3)**. Among 42 patients, 47 vascular procedures were performed (mean, 1.12 per patient). Due to vessel inflammation causing vessel stenosis or occlusion, intravascular stenting implantation was done in 29 patients (40%)and simple balloon angiography was performed in 5 patients (7%). Ten (34.5%) of the 29 patients with stenting implantation occurred post-interventional restenosis. The mean time of restenosis was (27.8±22.2) months (range2-72months) following intervention. **Table 6** shows the incidence of post-interventional vascular restenosis according to the lag time from stenting implantation. Post-interventional restenosis occurred most frequently within the first year after intervention (50%); the incidence had an tendency to decrease as time passed. In this study, we made the comparision of mean age, ESR, CRP of patients with intervention, post-interventional restenosis and non-intervention **(Table5)**. There was no significance difference of two groups in mean age, ESR and CRP (P>0.05).

Table 5. Comparision of mean age, ESR, CRP of patients with intervention, post-interventional restenosis and non-intervention.

Type	Intervention stenting implantation (n=29)	Restenosis after intervention stenting implantation (n=10)	Non-intervention stenting implantation (n=44)	p value
Mean age(years)	32.3±10.9	31.4±11.7	35.4±11.2	0.25
ESR(mm/h)	21.4±18.4	20.9±18.1	22.2±19.2	0.47
CRP(mg/dl)	1.1±1.3	1.1±1.7	1.1±1.6	0.98

* p<0.05 is statistically significant.

Table 6. Incidence of post-interventional vascular restenosis according to the lag time from stenting implantation

Lag time	Vascular intervention	
	Stenting implantation (n)	Restenosis (n,%)
<1year	8	4(50.0%)
1-2year	5	2(40.0%)
2-3year	4	1(25.0%)
3-4year	3	1(33.3%)
4-5year	4	1(25.0%)
5-6year	0	0
>6year	5	1(20.0%)
Total	29	10(34.5%)

Indications for surgery include hypertension with critical renal artery stenosis, extremity claudication limiting activities of daily living, cerebrovascular ischaemia or critical stenoses of three or more cerebral vessels, moderate aortic regurgitation, and cardiac ischemia with confirmed coronary artery involvement[2]. Table3 shows that three patients (4%) had unilateral nephrectomy for a nonfunctional kidney that were associated with renal artery stenosis and severe hypertension. Only one patient (1%) had renal autotransplatation because of artery lesions involving more than one branch. When anginal pain and significant coronary stenosis are present, coronary revascularization should be performed[13-14]. Bypass surgery is the standard technique[15].One patient (1%)with Takayasu arteritis (TA) was performed by coronary artery bypass grafting (CABG); Five patients (7%) with post-interventional restenosis managed to be performed by intravascular balloon angiography; Eight patients (11%) were performed by bypass or blood vessel prosthesis.

DISCUSSION

Takayasu arteritis (TA), which is a multifactorial and unknown cause disease, occurred most frequently in Asian young women. Previous study[16-20] has demonstrated that the major pathogenesis of TA involved four factors, including infection, genetic factors including HLA and other genes, autoimmunity, and sex hormones. TA causes various types of aortoarterial stenosis/occlusion or dilatation, so the clinical features are varied because of presence of the steno tic or occlusive artery lesions, such as the aortic

arch, descending thoracic or abdominal aorta, renal arteries, coronary arteries, and pulmonary arteries. Its incidence differs by race/ethnicity and geographical area. In Japan, young female patients are predominant, although it is reportedly distributed worldwide. However it is rare in white people[21]. The ratio of female to male patients with TA in Asian countries is higher than that in Africa, Western Europe, and North America. In this study, we reported that the ratio of female to male was 1:3.8, which was lower than that found (1:9) elsewhere [22].

In the present study, the median age at onset of first symptoms of the disease being 26 years is similar to that seen in Asian countries [23-26]. In the early stage, Takayasu arteritis (TA) had no typical clinical signs and symptoms, thus from the onset of first symptoms to diagnosis of disease often required for a long-term period. Two thirds of the patients had nonspecific manifestation in the early stage. Diagnosis is often delayed, particularly in the pediatric population[27].In Kerr's[2] research, the median delay in diagnosis is longer for pediatric patients than that of adults. Patients often had symptoms for several months before the diagnosis of TA was made. Nonspecific features include fever, night sweats, malaise, arthralgia or myalgia, and mild anaemia[5]. As the inflammation progresses and stenosis develop, the more characteristic features become apparent, influenced by the development of collateral circulation. Most patients had hypertension at disease onset before diagnosis of Takayasu arteritis. In our series of patients, there were 52% of patients with hypertension associated with the presence of renal artery stenosis or occlusion. Clinical features of patients with TA were not apparent in the early stage. In our study, the most common clinical manifestations were vascular bruits (71%), hypertension (69%), dizziness (59%) and Asymmetric blood pressure (53%). The age at disease onset among 51 of 73 patients with TA was less than 40 years old. So, for young patients, especially for pregnant women patients, if they have these clinical features, we should firstly take Takayasu arteritis into consideration.

Takayasu arteritis (TA) had nonspecific markers for diagnosis. Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are strong indicators of an underlying inflammatory process, such as vacuities; so, it is useful that both shortened the diagnostic delay of TA and monitored disease activity. In previous study[28], it had discovered that two independent risk factors associated with a higher probability of a diagnosis delay of ≥2 years: age <15 years and an ESR<30 at onset. But, the increasing level of ESR and CRP should not rule out the possibility of TA, since vascular damage can progress even in the absence of systemic inflammatory alterations[29],even so some experts thought that ESR and CRP still contributed to guiding the treatment and evaluating disease activity for patients with TA. In other researches[30-31], it was reported that Matrix metalloproteinase are useful markers of disease activity and helpful in diagnosing TA, but they all lack sensitivity and specificity.

Angiography is still the gold standard for diagnosis. However modern noninvasive diagnostic modalities including computed tomography scanning and magnetic resonance angiography, which have replaced angiography, allow an early and easy detection of the details of vascular lesions in 3-dimensional images[32-33], CT and MRI provide us with useful information for the early diagnosis and management of TA. Such techniques may allow earlier diagnosis and more accurate assessment of response to treatment than conventional clinical assessment and/or angiography, and monitor the progress of disease, but they also have some limitations in detecting lesions of visceral and renal arteries and the supra-aortic trunk. Angiography can find the vessel lumen of the pathological changes in the late stage of TA, including gradually stenotic section, the vessel lumen occlusion and expansion of aneurysm. However, if any these pathological changes can't also exclude the existing disease, especially in the early stage of TA[34]. In the present, we often adopt the Kerr's classification criteria according to Angiographic findings. During the study, Fifty-eight patients had underwent different angiographies, which showed more than one artery was affected among patients with Takayasu arteritis (TA).We found that the most common affected artery was the subclavian artery (40%), then was renal artery (27%).These arteries presented that the predominant anatomic lesion was stenosis or occlusion.

According to the treatment guideline[35], Glucocorticoids is still used for first-line treatment of Takayasu arteritis (TA). At the same time, antiplatelet therapy was used for patients with TA, aspirin was used by 70 of 73 patients and clopidogrel by 3 patients. In a multivariate model, it demonstrated that antiplatelet therapy was associated with a reduction of arterial ischemic events over time. Patients with TA generally respond well to glucocorticoids. The ratio of effective treatment ranged from 20% to 100% in previous study[2]. However, some patients exhibit resistance to glucocorticoid, especially for patients with HLA-B52[36]. In the retrospective study, one half of the patients received glucocorticoids alone or in combination with immunosuppressive agents for active disease. Evaluation of the disease activity was based on NIH criteria[2], especially monitoring the ESR and CRP. These criteria are used to manage the amount and duration of immunosuppressive therapy in clinical practice. However, they often underestimate the percentage of patients with active disease[37].Recently, treatment with mycophenolate mofetil[38], anti-tumor necrosis factor (TNF-α) therapy[39], and9 peripheral stem cell transplantation[40] have been attempted. However, these drugs can lead to severe ARDs for patients, such as bone marrow suppression and renal disorder, as well as the increased risk of infection in patients using these drugs together with glucocorticoids.

Endovascular interventional treatment was acknowledged to be a sensible method of treatment for vaso-occlusive disease, including percutaneous balloon angiography and stenting implantation[41]. The main indications for intervention were renal vascular hypertension, cerebral hypo perfusion, and limb claudication. Through the interventional therapy, clinical signs and symptoms of most patients was obtained in remission. In this study, ten patients after intervention occurred to restenosis and six cases occurred within 1-2 years. This shows interventional therapy for chronic TA patients has the definite curative effect, but long-term efficacy remains to be studied further. In terms of surgical treatment, not all patients with TA require to perform surgical treatment.

The major surgical procedures were aortocervical bypass, cervicosubclavian bypass, aortic replacement, aortocoronary bypass, replacement of aortic aneurysm, aortoaortic bypass, aortorenal bypass, reconstruction of renal vessel, and nephrotomy[42]. Surgical treatment of occlusions or stenosises and dilatations due to TA should in principle be performed during periods in which patients do not exhibit severe inflammation and are not on glucocorticoids therapy. As the affected lesions led to severe signs and symptoms, surgical treatment needs to be performed promptly. In the retrospective study, Hypertension is a common occurrence in TA and is related to major complications such as congestive heart failure, cardiomyopathy, hemorrhagic stroke, hypertensive encephalopathy, and myocardial infarction[30,42]. Renal artery stenosis as well as atypical coarctation or reduced elasticity of the arterial wall. Surgical bypass procedure for the treatment of TA has good curative effect, high safety, and the rate of restenosis is far lower than that of balloon angiography[43].

CONCLUSION

Takayasu arteritis is a nonspecific autoimmune and rare disease. It is very difficult to discover and diagnose this disease in the early stage. Especially for young women patients(age<40years), if they have nonspecific features including unknown fever, night sweats , weight loss and vascular bruits, the clinician should not rule out the possibility of TA. So, physicians should raise awareness of it and apply to appropriate methods for early diagnosis in TA patients as soon as possible.

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CONFLICT OF INTEREST

All the authors were involved in the study.

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