Aneurysms in Takayasu's arteritis: a retrospective study of Chinese patients

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ABSTRACT

Objective. *Aneurysm formation can cause life-threatening complications in Takayasu's arteritis (TAK). The objective of this study was to evaluate the demographic, clinical and angiographic features, and outcomes of aneurysm secondary to TAK in Chinese patients.*

Methods. *The medical charts of patients diagnosed with TAK in Changhai Hospital between 2001 and 2017 were retrospectively reviewed.*

Results. *Aneurysms were identified in 66 (16.6%) of 397 patients with TAK. The mean age at onset was 30.4±11.5 years, with a male:female ratio of 1:2.7. Patients with aneurysm had a higher proportion of male ($p<0.01$), higher incidences of bruit, chest tightness and aortic regurgitation (all $p<0.001$), and a lower incidence of visual disturbances ($p<0.01$) as compared with patients without aneurysm. The prevalence of elevated ESR and CRP and ITAS2010 score were higher in patients with than without aneurysm (all $p<0.01$). Angiographic classification showed that type V (30.3%) was the most frequent pattern in patients with aneurysm though Type I was dominant in patients without aneurysm. Multiple aneurysms were found in 30.3% of patients and the most common site of aneurysms was abdominal aorta (22.1%). Glucocorticoids were prescribed in 86.4% of patients with aneurysm, and surgical procedures were performed in 80.3%. Five out of 52 patients died during the median 3-year follow-up period.*

Conclusion. *These findings could provide useful information on the demographical, clinical and angiographic features of TAK patients with aneurysm. Aneurysm formation in TAK may be associated with male gender and active vascular inflammation.*

Introduction

Takayasu's arteritis (TAK) is a chronic, large-vessel vasculitis of unknown aetiology that primarily affects the aorta and its main branches (1). Although TAK has a worldwide distribution, the disease is more common in east Asian and middle eastern countries, usually affecting women younger than 40 years (2). It is characterised by granulomatous inflammation in the adventitia and medial wall of the involved arteries (3). Fibrosis develops gradually as the disease progresses, followed by stenosis or occlusion in the lesions. Occasionally, the destruction of the elastica and muscularis may result in artery dilatation or aneurysm formation (1, 4). The clinical presentations of TAK vary greatly depending on the affected arteries and the degree of disease progression. The patterns of arterial involvement, disease expression and prognosis also seem to be different in various ethnic populations (5-18).

The formation of aneurysms may progress to heart failure due to aortic valve regurgitation or aneurysm rupture, which is a potentially life-threatening risk factor in TAK. However, the estimated incidence of aneurysms in patients with TAK is variable in different populations and genders, and the clinical features of TAK patients with aneurysm are still not fully clarified (13-23). This retrospective study was conducted to evaluate the epidemiological, clinical, angiographic and prognostic features of aneurysm associated with TAK in Chinese patients from Changhai hospital.

Materials and methods

Patient population

In this single-centre retrospective study, the medical records of 397 patients diagnosed with TAK in Changhai Hospital, Shanghai, China between January 2001

and December 2017 were reviewed. All patients fulfilled the 1990 American College of Rheumatology criteria for TAK (24). Other causes of aortic abnormalities were excluded on clinical grounds. These included atherosclerosis, infectious aortitis (*e.g.* syphilis, tuberculosis), systemic inflammatory diseases (*e.g.* Behçet's disease, Cogan syndrome, giant cell arteritis) and congenital diseases (*e.g.* Marfan syndrome, Ehlers-Danlos syndrome). The study was approved by the ethics committee of Changhai Hospital. Written informed consent was waived due to the retrospective nature of this study.

Data collection

Data were collected using a form specifically designed for this study. The information extracted included: demographic features, clinical history of TAK (signs and symptoms at onset, at time of diagnosis and during the course of the disease), comorbidities, laboratory parameters, imaging findings and medical and surgical treatments. Histological specimen was obtained wherever possible, but was not essential for inclusion. The vascular lesions were evaluated with various imaging modalities. Aneurysm was defined as a localised dilatation of the aortic diameter by at least 50% of its normal value (19, 21), and pseudoaneurysm was excluded. Among 397 patients, all but 14 patients underwent systemic angiographic assessment at the time of diagnosis by conventional angiography, computed tomography angiography (CTA) or magnetic resonance angiography (MRA). In the remaining 14 patients, 12 patients were initially diagnosed by Doppler ultrasonography and 2 patients by positron emission tomography (PET)-CT. The evaluation of intracranial, pulmonary, or coronary arteries were performed in patients with suspected involvement of the corresponding vessel. However, this may underestimate the prevalence of aneurysms if the aneurysmal lesion is not severe enough to cause clinical symptoms. Transthoracic echocardiography was performed to detect the presence of aortic regurgitation.

Angiographic classification was made according to the criteria established in 1994 (25). Type I involves the branches of the aortic arch; Type IIa involves the ascending aorta, aortic arch and its branches; Type IIb involves the ascending aorta, aortic arch and its branches, and thoracic descending aorta; Type III involves the thoracic descending aorta, abdominal aorta, and/or renal arteries; Type IV involves the abdominal aorta and/or renal arteries; and Type V combines the features of Type IIb and IV.

Disease activity was evaluated according to the Indian Takayasu Clinical Activity Score (ITAS2010) (26). The ITAS2010 is a TAK-specific disease activity tool and contains 44 items in six systems. New manifestations or manifestations that have worsened during the last 3 months are scored.

Statistical analysis

Data were expressed as mean ± standard deviation (SD) or median (Q1, Q3) for continuous variables and total number (percentage) for categorical variables. Comparisons between groups were performed using independent *t* test, Mann-Whitney test, χ^2 test or Fisher's exact test as appropriate. *p*-values less than 0.05 were considered statistically significant. All analyses were carried out with the SPSS software (v. 19.0, IBM, Armonk, NY, USA).

Table I. Demographic profiles of TAK patients with and without aneurysm.

	Patients with aneurysm n=66	Patients without aneurysm n=331	*p*-value
Sex, n. (%)			
Male	18 (27.3%)	46 (13.9%)	0.007
Female	48 (72.7%)	285 (86.1%)	0.007
Age at onset, years			
Mean ± SD	30.4 ± 11.5	29.5 ± 11.9	0.573
≤18, n. (%)	8 (12.1%)	56 (16.9%)	0.333
19–40, n. (%)	43 (65.2%)	220 (66.5%)	0.837
>40, n. (%)	15 (22.7%)	55 (16.6%)	0.234
Duration at time of aneurysm detection, years			
Median (Q1, Q3)	2.0 (1.0, 5.0)		

Results

Demographic features

Aneurysms were present in 66 (16.6%) of 397 patients with TAK (Table I). Among them there were 18 males and 48 females with a male:female ratio of 1:2.7. The mean age at disease onset was 30.4±11.5 years, and 15 patients (22.7%) had disease onset after 40 years of age. The median duration of the disease at the time of aneurysm detection was 2.0 (1.0, 5.0) years.

The proportion of male patients was higher in TAK patients with (18/66, 27.3%) than those without (46/331, 13.9%) aneurysm (p=0.007; Table I). No significant differences were found between the two groups in the distribution of age at onset.

Clinical features

The clinical manifestations of TAK patients with and without aneurysm are shown in Table II. In patients with aneurysm, constitutional symptoms such as fatigue, fever and weight loss were found in 39.4% of patients. Vascular signs or symptoms were common (95.5%) and included hypertension (66.7%), diminished or absent pulse (65.2%), vascular bruit (62.1%), asymmetric blood pressure (60.6%), extremity pain and claudication. Neurological symptoms were present in 62.1% of patients, the most frequent being dizziness (42.4%) and headache (37.9%). Cardiac symptoms occurred in 36.4% of patients, with chest tightness being the most prominent cardiac complaint (30.3% of patients). Arthralgia and skin rash were less common (3.0%).

Compared with TAK patients without aneurysm, vascular bruit, chest tightness and aortic regurgitation were more common (all p<0.001) and visual disturbances were less observed (p=0.001) in patients with aneurysm (Table II). Otherwise, there was no statistical difference in the clinical symptoms and signs between the two groups.

Table II. Comparison of clinical characteristics between 66 patients with aneurysm and 331 patients without aneurysm in TAK.

	Patients with aneurysm n. (%)	Patients without aneurysm n. (%)	*p*-value
Constitutional symptoms	26 (39.4%)	163 (49.2%)	0.143
Fatigue	20 (30.3%)	126 (38.1%)	0.232
Fever	7 (10.6%)	46 (13.9%)	0.473
Weight loss	2 (3.0%)	11 (3.3%)	1.000
Vascular findings	63 (95.5%)	326 (98.5%)	0.132
Hypertension	44 (66.7%)	190 (57.4%)	0.162
Diminished or absent pulse	43 (65.2%)	243 (73.4%)	0.172
Bruit	41 (62.1%)	119 (36.0%)	<0.001
Asymmetric blood pressure	40 (60.6%)	209 (63.1%)	0.697
Extremity pain	4 (6.1%)	17 (5.1%)	0.763
Claudication	2 (3.0%)	18 (5.4%)	0.549
Neurological findings	41 (62.1%)	257 (77.6%)	0.008
Dizziness	28 (42.4%)	175 (52.9%)	0.121
Headache	25 (37.9%)	87 (26.3%)	0.056
Stroke	8 (12.1%)	63 (19.0%)	0.181
Visual disturbances	4 (6.1%)	84 (25.4%)	0.001
Syncope	4 (6.1%)	43 (13.0%)	0.112
Cardiac findings	24 (36.4%)	54 (16.3%)	<0.001
Chest tightness	20 (30.3%)	33 (10.0%)	<0.001
Aortic regurgitation	12 (18.2%)	15 (4.5%)	<0.001
Palpitation	9 (13.6%)	22 (6.6%)	0.053
Chest pain	5 (7.6%)	18 (5.4%)	0.561
Arthralgia, skin rash	2 (3.0%)	17 (5.1%)	0.752
Comorbidities			
Smoker	1 (1.5%)	4 (1.2%)	1.000
Active/latent tuberculosis	2 (3.0%)	8 (2.4%)	0.675
Diabetes mellitus	1 (1.5%)	8 (2.4%)	1.000
Dyslipidaemia	16 (24.2%)	58 (17.5%)	0.201
Laboratory findings			
Elevated ESR	43 (65.2%)	152 (45.9%)	0.004
Elevated CRP	42 (63.6%)	148 (44.7%)	0.005
Anemia	24 (36.4%)	104 (31.4%)	0.433
ITAS2010 score	9.26 ± 3.24*	7.92 ± 3.31*	0.003
Angiographic classification			
Type I	17 (25.8%)	138 (41.7%)	0.015
Type IIa	9 (13.6%)	15 (4.5%)	0.009
Type IIb	3 (4.6%)	11 (3.3%)	0.712
Type III	4 (6.1%)	14 (4.2%)	0.517
Type IV	13 (19.7%)	73 (22.1%)	0.671
Type V	20 (30.3%)	80 (24.2%)	0.295

*Mean ± SD.
ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ITAS2010: Indian Takayasu Clinical Activity Score.

Of the 66 patients with aneurysm, one was smoker, 2 had active or latent pulmonary tuberculosis, 1 had diabetes mellitus, and 16 had dyslipidemia. These comorbidities showed no statistical difference between TAK patients with and without aneurysm.

Laboratory and histologic findings

Elevated erythrocyte sedimentation rate (ESR) (>20 mm/h) was noted in 65.2% and elevated C-reactive protein (CRP) (>10 mg/l) in 63.6% of TAK patients with aneurysm at the first visit. Anaemia was found in 36.4% of them. Elevated ESR and CRP were more prevalent in patients with aneurysm compared with patients without aneurysm (p=0.004 and p=0.005, respectively; Table II).

Of 66 patients with aneurysm, 65 (98.5%) had active TAK according to ITAS2010 score ≥2 at the first visit, and the majority of patients without aneurysm (325/331, 98.2%) also had active disease. However, the ITAS2010 score was higher in patients with than those without aneurysm (p=0.003; Table II).

Biopsy specimens were obtained during surgery from 6 patients with aneurysm. The ITAS2010 score of them was 6.5±3.4 and histological material showed evidence of aorto-arteritis in all cases.

Angiographic findings

By using the 1994 angiographic classification for TAK, type V (30.3%) was the most frequent involvement pattern in patients with aneurysm followed by type I (25.8%), type IV (19.7%) and type IIa (13.6%), whereas type III (6.1%) and type IIb (4.6%) were uncommon (Table II). Type I was dominant in patients without aneurysm and less common in patients with than without aneurysm (p=0.015). In contrast, type IIa was more common in patients with than without aneurysm (p=0.009).

The distribution of arterial involvement of TAK patients with aneurysm is presented in Table III. A total of 95 aneurysms were detected in our cohort and 20 (30.3%) of 66 patients had multiple aneurysms. The abdominal aorta (22.1%) was the most common site of aneurysms, followed by carotid arteries (21.1%) and ascending aorta (18.9%). Stenosis or occlusion occurred in all patients with aneurysm and was most frequently observed in the carotid arteries (17.0%) and renal arteries (15.0%).

Treatment

Glucocorticoids were prescribed in 57 (86.4%) of TAK patients with aneurysm and immunosuppressive agents in 10 (15.2%). Methotrexate, cyclophosphamide and mycophenolate mofetil were used in 4, 3 and 3 patients, respectively. Antiplatelet (36, 54.5%) or anticoagulant (12, 18.2%) drugs were prescribed in 45 patients (68.2%).

Sixty-three surgical procedures were performed in 53 patients with aneurysm (80.3%), of whom 46 began prednisone treatment before surgical interventions and 7 received immunosuppressive agents after surgical procedures. Percutaneous transluminal angioplasty alone (4 cases) or angioplasty plus stenting was performed in 31 (47.0%) of the patients, a bypass in 17 (25.8%), and aneurysm repair in 15 (22.7%).

Table III. Vascular involvement in 66 TAK patients with aneurysm.

Vessel	Aneurysm n. (%)	Stenosis / Occlusion n. (%)	Any lesion n. (%)
Intracranial artery	1 (1.1%)	1 (0.4%)	2 (0.6%)
Carotid artery	20 (21.1%)	43 (17.0%)	63 (18.1%)
Vertebral artery	3 (3.2%)	16 (6.3%)	19 (5.5%)
Subclavian artery	6 (6.3%)	30 (11.9%)	36 (10.3%)
Innominate artery	2 (2.1%)	9 (3.6%)	11 (3.2%)
Axillary artery	0	5 (2.0%)	5 (1.4%)
Ascending aorta	18 (18.9%)	16 (6.3%)	34 (9.8%)
Aortic arch	4 (4.2%)	10 (4.0%)	14 (4.0%)
Thoracic descending aorta	9 (9.5%)	19 (7.5%)	28 (8.0%)
Pulmonary artery	1 (1.1%)	4 (1.6%)	5 (1.4%)
Abdominal aorta	21 (22.1%)	29 (11.5%)	50 (14.4%)
Mesenteric artery	0	7 (2.8%)	7 (2.0%)
Renal artery	7 (7.4%)	38 (15.0%)	45 (12.9%)
Iliac artery	2 (2.1%)	18 (7.1%)	20 (5.7%)
Femoral artery	1 (1.1%)	8 (3.2%)	9 (2.6%)

Outcomes

Fifty-two (78.8%) of the TAK patients with aneurysm were followed for a median duration of 3.0 (1.0, 7.0) years. One patient developed endoleakage following endovascular procedure. Five patients (9.6%) died during the follow-up period. The causes of death were post-operative complications in two, ruptured aneurysm in two, and congestive heart failure in one patient.

The median duration of follow-up for the other 252 patients without aneurysm was 4.0 (2.0, 7.0) years. Twenty-five deaths occurred (9.9%) during the follow-up. There was no significant difference in the follow-up period and mortality rate between patients with and without aneurysm.

Discussion

TAK is a primary arteritis of unknown aetiology involving the vessel walls that leads to wall thickening, luminal stenosis or occlusion, and aneurysm formation (1). Although stenotic lesions are identified most frequently, aneurysm formation can cause fatal complications including heart failure and aneurysm rupture in TAK. To our knowledge, this is the largest single-centre cohort of TAK patients with aneurysm so far studied in China.

The incidence of aneurysm formation in previous reports about patients with TAK varies markedly, which is likely to be related to sample size, ethnic susceptibility and single-centre source of patients. Several large series from France (12.2%), Mexico (10%), India (9.1%) and Italy (7%) reported similar incidence of aneurysm associated with TAK (13-15, 23), though a higher incidence (47%) of aneurysms was reported in a South African cohort (18). Aneurysms were identified in 32% of the patients with TAK in a Japanese cohort (22) but noted in only 15% of Japanese patients in another cohort comprising 1372 newly registered TAK patients using nationwide registration forms (16). In the present study, aneurysms were identified in 16.6% of the patients with TAK admitted to our hospital from 2001 to 2017, which was similar to that reported in most studies but 4-fold higher than in two studies from China (17, 21). This difference may be due to the selection process and imaging modalities and suggests that the incidence of aneurysms in Chinese TAK patients could be underestimated. In our series, most patients were from surgical department and considerable information was obtained by MRA or CTA, which might improve the detection rate of aneurysms. Moreover, the sample size of our TAK cohort com-

Table IV. Location of aneurysms in TAK patients from different populations.

	Li *et al.* (17) n. (%)	Mwipatayi *et al.* (18) n. (%)	Sueyoshi *et al.* (19) n. (%)	Kumar *et al.* (20) n. (%)	Yang *et al.* (21) n. (%)	Matsumura *et al.* (22) n. (%)
Carotid artery	3 (9.1%)	24 (6.9%)	–	2 (3.4%)	0	1 (1.8%)
Vertebral artery	1 (3.0%)	–	–	–	–	–
Subclavian artery	5 (15.2%)	22 (6.4%)	–	7 (11.9%)	1 (1.8%)	7 (12.3%)
Innominate artery	1 (3.0%)	21 (6.1%)	–	1 (1.7%)	0	2 (3.5%)
Ascending aorta	3 (9.1%)	50 (14.5%)	2 (11.8%)	3 (5.1%)	18 (31.6%)	16 (28.1%)
Aortic arch	1 (3.0%)	45 (13.0%)	3 (17.6%)	2 (3.4%)	7 (12.3%)	3 (5.3%)
Thoracic descending aorta	3 (9.1%)	60 (17.3%)	1 (5.9%)	18 (30.5%)	5 (8.8%)	11 (19.3%)
Pulmonary artery	0	11 (3.2%)	–	–	–	8 (14.0%)
Abdominal aorta	10 (30.3%)	71 (20.5%)	8 (47.1%)	18 (30.5%)	15 (26.3%)	7 (12.3%)
Mesenteric artery	0	9 (2.6%)	–	0	0	–
Renal artery	2 (6.1%)	15 (4.3%)	–	3 (5.1%)	1 (1.8%)	1 (1.8%)
Iliac artery	4 (12.1%)	13 (3.8%)	–	2 (3.4%)	0	1 (1.8%)
Femoral artery		–	–	2 (3.4%)	–	–
Celiac artery	–	–	–	0	1 (1.8%)	–
Coronary artery	0	–	–	1 (1.7%)	–	–
Aortic bifurcation	–	5 (1.4%)	–	–	–	–
Aortic root	–	–	–	–	9 (15.8%)	–
Ascending aorta to descending aorta	–	–	1 (5.9%)	–	–	–
Aortic arch to descending aorta	–	–	2 (11.8%)	–	–	–
Total	33	346	17	59	57	57

prising 397 patients was much larger than that of the study by Cong *et al*. (9), in which 6 aneurysms were identified in 125 patients from our hospital between 1993 and 2008 and a small number of patients were included in the present study.

Our study showed a higher proportion of male in TAK patients with than those without aneurysm, which is in line with the study of Watanabe *et al*. (16). Tobacco smoking appears not to be the major reason for the frequent development of aneurysms in male patients with TAK. Smoking was observed in 10 of 14 male patients with aneurysm in a Chinese TAK cohort (21), while only 1 of 18 male patients with aneurysm was smoker in our series. In the present study, we found no significant difference in the age at onset between patients with and those without aneurysm. Moreover, aneurysms were noted even in pediatric patients (12.1%), and the interval between TAK onset and aneurysm detection was only about two years. These data suggest that aneurysm formation is not a late manifestation of TAK.

It is believed that the weakened aortic wall becomes an aneurysm when vascular inflammation results in the degeneration of the media in TAK (27). In our study, TAK patients with aneurysm had higher incidences of bruit, chest tightness and aortic regurgitation and a lower incidence of visual disturbances when compared with patients without aneurysm, though the prevalence of systemic symptoms and signs was similar between the two groups. Intriguingly, the prevalence of elevated ESR and CRP and ITAS2010 score, a new tool for disease assessment, were higher in TAK patients with than without aneurysm, suggesting that vascular inflammation could be more intense in patients with aneurysm. However, active vascular inflammation may be ongoing for many years, even in the absence of clinical or biological activities (28). MRI and ^{18}F-FDG PET are now promising for the assessment of inflammation activity and response to treatment (29-31).

Hypertension is frequently observed in patients with TAK but poorly considered to be a major cause of the formation of aneurysms. Some patients with aneurysm did not have high blood pressure. Furthermore, no significant difference in the incidence of hypertension was detected between patients with and those without aneurysm in our series. Similar findings were also reported by other groups (19, 20). Nevertheless, Sueyoshi *et al*. showed that the growth of aortic aneurysms measured with CT in TAK might be related to blood pressure (19), supporting hypertension as a possible promoting factor of aneurysm formation.

The angiographic involvement pattern of TAK patients revealed variations in different series and either type V or type I was the most frequent (5-11, 14-17). In our series, Type I (the branches of the aortic arch) was dominant in patients without aneurysm and type V (the combined features of the other types) was the most common pattern in patients with aneurysm. Another characteristic feature of patients with aneurysm was their relatively high proportion of type IIa (the ascending aorta, aortic arch and its branches) and low proportion of type I. Our findings suggest that TAK patients with aneurysm tend to have more extensive aortic involvements.

Aneurysms could be located in the various sites of the aorta in patients with TAK. Table IV shows the location of aneurysmal lesions in TAK described by other authors. Consistent with several previous studies (17-20), the abdominal aorta was found to be the most frequent aortic site involved in aneurysms in our study. However, another two studies showed that aneurysms were most commonly observed in the ascending aorta (21, 22). More studies are needed to clarify this issue. Additionally, aneurysmal disease without any vascular stenosis or occlusion was not found in the present study but has been reported by Mwipatayi *et al*. (7%) (18), suggesting that aneurysms in TAK could be an initial manifestation and is not necessarily a change secondary to stenotic lesions.

Despite the slow growth of aneurysms in most patients with TAK, rapid enlargement of some aneurysms can lead to rupture, which is recognised as a fatal complication of TAK (19). Thus, an aneurysm once observed needs intensive follow-up and surgical treatment is mandatory before it ruptures. In our series, the majority of TAK patients with aneurysm underwent surgical procedures and received perioperative glucocorticoids and the outcomes were generally satisfactory. Surgical interventions in TAK are usually performed when disease is judged to be quiescent (32). In spite of this, approximately 50% of arterial biopsy specimens taken during such procedures show active inflammation (9, 33), highlighting the discrepancy between clinical assessment and actual disease activity. The histologic evidence of covert active inflammation confirms the argument for perioperative immunosuppressive therapy for patients with TAK. It has been reported that perioperative corticosteroid therapy could improve surgical results of aneurysm secondary to TAK (34).

The major limitation of the current study is its retrospective nature with a low follow-up rate. Therefore, the findings may have some bias. Another weak point of this study is that it was based on a single centre database. There was also a lack of standardised protocol to assess the arterial lesions. Prospective multi-centre longitudinal studies are needed to further evaluate the development of aneurysms in patients with TAK.

Conclusions

The incidence of aneurysms in our Chinese cohort of TAK patients was 16.6%. Male patients appeared to develop aneurysms more frequently. Vascular inflammation in TAK patients with aneurysm could be not only intense but also extensive and thereby contributes to aneurysm formation.

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