ORIGINAL ARTICLE

Retrospective analysis of 95 patients with large vessel vasculitis: a single center experience

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Abstract

Aim: Although Takayasu arteritis (TAK) and giant cell arteritis (GCA) have been considered as distinct disease entities, similarities of these diseases have been recently reported. However, little data is available regarding this issue in Japanese patients with TAK and GCA. In addition, the classification criteria for TAK established in 1990 by the American College of Rheumatology (ACR) have been criticized due to the age restriction for disease onset (≤ 40 years). Thus, we aimed to compare the clinical characteristics of Japanese patients with TAK and those with GCA and to clarify whether clinical differences existed between patients with early-onset (≤ 40 years) and late-onset (> 40 years) TAK.

Methods: We enrolled 86 patients with TAK and nine with GCA who visited our department from 1990 to 2014. The diagnoses of TAK and GCA were based on the criteria of the Japanese Circulation Society and the ACR, respectively.

Results: Mean ages at onset for TAK and GCA were 36.4 and 71.0 years, respectively. Patients with TAK had significantly higher incidences of aortic regurgitation and carotid and subclavian arterial involvement, lower frequencies of polymyalgia rheumatica, and better prognoses than those with GCA. In contrast, the clinical characteristics, distribution of arterial lesions, treatments administered, and prognoses of patients with early- and late-onset TAK were comparable.

Conclusions: These results suggested that TAK and GCA differed substantially, and that the age restriction (≤ 40 years) may not be necessary for the diagnosis of TAK.

Key words: giant cell arteritis, large vessel vasculitis, Takayasu arteritis.

INTRODUCTION

Large vessel vasculitis (LVV) as part of the vasculitis syndrome affects the aorta and its major branches.[1] Takayasu arteritis (TAK) and giant cell arteritis (GCA) are the two major variants of LVV.[1] The exact mechanisms underlying these diseases remain unclear; however, chronic autoimmune inflammation of the arterial walls plays a pivotal role in their pathogenesis.[2] Chronic inflammation of blood vessels leads to stenosis, occlusion, dilatation or aneurysmal formation, which results in serious organ damage, such as aortic regurgitation (AR), renovascular hypertension, ischemic optic neuropathy (ION), cerebral infarction, hearing loss and other conditions.[3]

Historically, TAK and GCA have been considered as distinct disease entities due to differences in their age at

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onset, predilection for arterial involvement, and association of polymyalgia rheumatica (PMR); however, similarities between TAK and GCA have been recently reported.[3,4] For example, the histopathologic features of TAK and GCA are indistinguishable.[1] In addition, aortic involvement is prevalent even in GCA, and the distribution of affected arteries is quite similar between TAK and GCA.[5–7] Therefore, some have suggested that they represent a spectrum within the same disease state.[5–7] This controversy remains unsettled; however, there is a paucity of data available regarding this issue in Japanese patients with TAK and GCA.

Although the classification criteria for TAK were established in 1990 by the American College of Rheumatology (ACR),[8] limitations pertaining to these criteria have long been noted.[9] The primary criticism regarding these criteria stems from the age restriction for disease onset ($\leq$ 40 years).[10] In clinical practice, patients who meet the criteria for TAK but do not fulfill those of GCA due to a lack of headaches and temporal arterial abnormalities are diagnosed with TAK irrespective of age at onset.[11,12] In 2008, the Japanese Circulation Society (JCS) Joint Working Group published new diagnostic criteria for TAK.[13] According to these new criteria, a definitive diagnosis of TAK requires imaging data, such as digital subtraction angiography, computed tomography (CT), and magnetic resonance angiography (MRA). Although the new criteria contain a description that TAK is prevalent among young woman, the age restriction has been excluded.[13] However, it remains unclear whether differences in the clinical characteristics between patients with early-onset ($\leq$ 40 years) and late onset (> 40 years) TAK exist.

Therefore, the aims of this study were to compare the clinical characteristics, arterial distributions and survival of Japanese patients with TAK and GCA and to clarify whether differences in the clinical features, arterial distributions, treatments administered and prognoses, exist between early- and late-onset patients with TAK.

MATERIALS AND METHODS
Study design and patient selection
We enrolled patients with TAK and GCA who visited our department from April 1990 to October 2014. The diagnosis of TAK was based on the diagnostic criteria of the JCS Joint Working Group,[13] while the diagnosis of GCA was based on the classification criteria of the ACR, as the JCS has not proposed new diagnostic criteria for GCA.[13,14] Patients who met the criteria for TAK

but did not fulfill the criteria for GCA due to a lack of headaches and temporal arterial abnormalities were diagnosed with TAK irrespective of age. Early- and late-onset TAK were distinguished from the age of initial symptoms (early, $\leq$ 40 years; late, > 40 years). The follow-up period was defined as the time from diagnosis to either the date of death or the latest visit to the hospital. Patient follow-up was conducted until October 2014.

Clinical evaluation
We retrospectively reviewed patient medical records and collected clinical data pertaining to age at onset, sex, symptoms and physical findings at diagnosis, complications, medications and surgical interventions. The pretreatment values of C-reactive protein and the erythrocyte sedimentation rate as well as the presence or absence of AR, ION or hypertension (blood pressure $\geq$ 140/90 mmHg) irrespective of cause at diagnosis were also investigated.

Evaluation of arterial lesions
Arterial involvement was defined as stenosis, occlusion, dilatation or wall thickening with delayed enhancement of the aorta or its major branches as evaluated by contrast-enhanced CT. The distribution of affected arteries was comprehensively determined using enhanced CT, MRA and fluorodeoxyglucose positron emission tomography (FDG-PET) to differentiate other conditions such as atherosclerosis.

Treatment
We initiated prednisolone at a dose of 0.5–1.0 mg/kg/day after a diagnosis of LVV when spontaneous remission was not obtained. If patients experienced a relapse or a progression of arterial lesions, methotrexate (MTX), cyclosporine A (CsA), other immunosuppressive agents or biologic agents were added, sometimes in combination.

Statistical analysis
Statistical analysis was performed using GraphPad Prism 5 (GraphPad, San Diego, CA, USA) and EZR software.[15] The Fisher's exact test was used for binary data and the Mann–Whitney *U*-test was used for continuous data. The survival and cumulative incidence curves were drawn using the Kaplan–Meier method for a maximum of 10 years in each patient, and the log-rank test was used to compare survival rates between patient groups. *P*-values < 0.05 were considered to be statistically significant.

RESULTS

Baseline characteristics of patients with TAK and GCA

A total of 95 patients were enrolled. Of these patients, 86 and nine were diagnosed with TAK and GCA, respectively. A temporal arterial biopsy was performed in seven patients with GCA. Baseline patient characteristics are shown in Table 1. The mean age at onset for patients with TAK and GCA was 36.4 and 71.0 years, respectively, and females were more predominant in TAK than in GCA. There were no statistically significant differences in inflammatory markers or the rates of hypertension or ION between the two groups; however, the prevalence of AR was significantly higher in patients with TAK compared with those with GCA (Table 1). When sorted by age at onset, the age-based distribution revealed that patients with TAK exhibited a bimodal distribution, while those with GCA showed only elderly onset (Fig. 1a).

Survival rates for TAK and GCA

The overall survival rates for patients with TAK were 97.7%, 97.7% and 95.3% at 1, 5 and 10 years, respectively (Fig. 1b). The survival rate for GCA was significantly lower than that for TAK (Fig. 1b), although it may not be appropriate to compare the survival rates because average ages of the two groups were significantly different. Causes of death included sudden death of unknown cause (two patients with TAK and one with GCA), infectious cerebritis (one patient with TAK) and esophageal cancer (one patient with GCA).

Complications of TAK and GCA

Various extravascular manifestations can occur in patients with LVV.[16] Table 2 shows the major complications observed in two or more patients with LVV. Thyroid dysfunction was the most common complication, followed by angina pectoris, ulcerative colitis and cerebral infarction. The incidence of PMR was significantly higher in patients with GCA compared with those with TAK.

Arterial distribution of TAK and GCA

Figure 1c shows the distribution of the affected arteries in patients with TAK and GCA. Aortic involvement was observed even in patients with GCA, especially in the descending and abdominal aortas; however, the rate of carotid and subclavian arterial involvement was significantly higher in patients with TAK compared with those with GCA (Fig. 1c).

Comparison of the clinical characteristics of patients with between early- and late-onset TAK

The clinical features of patients with early-onset (≤ 40, $n = 58$) and late-onset (> 40, $n = 28$) TAK were compared. All patients with early-onset TAK met the 1990 ACR criteria, while only 11 of 28 (39.3%) patients with late-onset TAK fulfilled these criteria. Table 3 shows the results of baseline comparisons of the clinical characteristics between the two groups. As expected, the mean age at onset in patients with late-onset TAK was significantly higher than in patients with early-onset TAK. No statistically significant differences were observed in gender, inflammatory markers, or the rates of AR or ION; however, patients with late-onset TAK had a significantly higher incidence of hypertension compared with those with early-onset TAK (Table 3).

Symptoms and physical findings at diagnosis were also compared between the two groups. Fever, general malaise, syncope and visual disturbances were included as symptoms, while differences in blood pressure between the two arms (≥ 10 mmHg), vascular bruit

Table 1 Comparison of the clinical characteristics between patients with TAK and those with GCA

	TAK	GCA	P
Cases (n)	86	9	
Age at onset (years $\pm$ SD)	36.4 $\pm$ 18.6	71.0 $\pm$ 8.7	< 0.001
Female, n (%)	79 (91.9%)	6 (66.7%)	0.051
CRP (mg/dL $\pm$ SD)	5.8 $\pm$ 7.2	7.4 $\pm$ 6.1	0.48
ESR (mm/h $\pm$ SD)	65.5 $\pm$ 47.0	64.8 $\pm$ 47.4	0.97
Hypertension, n (%)	34 (39.5%)	5 (55.6%)	0.48
Aortic regurgitation, n (%)	42 (48.8%)	0 (0%)	0.004
Ischemic optic neuropathy, n (%)	2 (3.4%)	1 (11.1%)	0.26

The values of age at onset, CRP, and ESR indicate mean $\pm$ SD. The P-values were determined by comparison between the two groups. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; TAK, Takayasu arteritis.
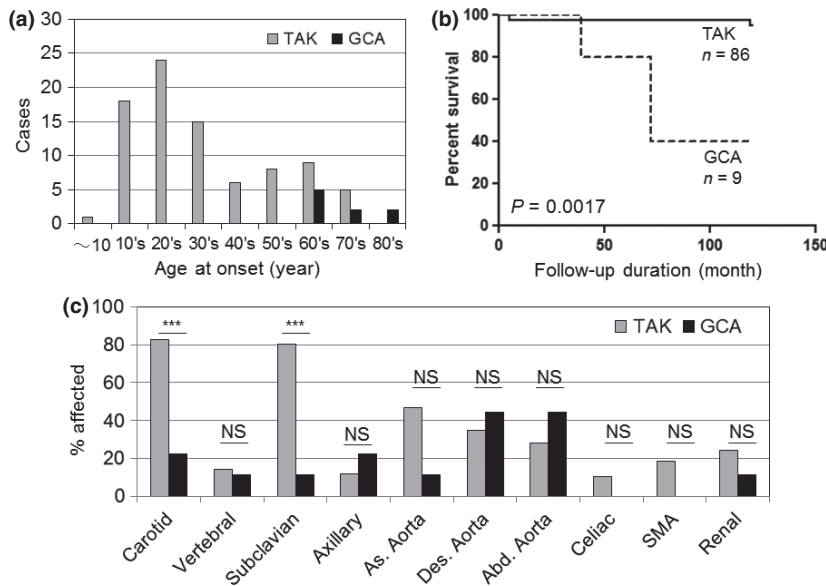
Figure 1 (a) Age-based distribution sorted by age at onset in patients with TAK and GCA. (b) Survival curves in patients with TAK and GCA. (c) Distribution of arterial involvement in patients with TAK and GCA. As. Aorta, ascending aorta; Abd. Aorta, abdominal aorta; Des. Aorta, descending aorta; GCA, giant cell arteritis; NS, not significant; SMA, superior mesenteric artery; TAK, Takayasu arteritis. ***P < 0.001.

Table 2 The major complications of patients with TAK or GCA

	TAK	GCA	P
Thyroid dysfunction, n (%)	12 (14.0%)	1 (11.1%)	1
Angina pectoris, n (%)	9 (10.5%)	0 (0%)	0.59
Ulcerative colitis, n (%)	7 (8.1%)	0 (0%)	1
Cerebral infarction, n (%)	7 (8.1%)	1 (11.1%)	0.56
Rheumatoid arthritis, n (%)	5 (5.8%)	1 (11.1%)	0.46
Hearing loss, n (%)	5 (5.8%)	0 (0%)	1
Crohn's disease, n (%)	2 (2.3%)	0 (0%)	1
Colon cancer, n (%)	2 (2.3%)	0 (0%)	1
Polymyalgia rheumatica, n (%)	0 (0%)	2 (22.2%)	0.008

P-values were determined by comparison between the two groups. GCA, giant cell arteritis; TAK, Takayasu arteritis.

and pulselessness were included as physical findings. There were no statistically significant differences in these symptoms or physical findings between the two groups (Fig. 2a). Moreover, the distribution of the affected arteries was also quite similar between the two groups (Fig. 2b). The rate of carotid arterial involvement alone was significantly higher in patients with early-onset TAK compared with those with late-onset TAK; however, when we compared the frequencies of stenosis in descending and abdominal aortas, stenotic lesions were more common in patients with early-onset TAK (descending, 6/21; abdominal, 8/17) than in patients with late-onset TAK (descending, 1/9; abdominal, 0/7). In contrast, the frequency of dilatation was higher in late-onset TAK patients (descending, 6/9;

abdominal, 5/7) compared with patients with early-onset TAK (descending, 5/21; abdominal, 3/17).

Medications in patients with TAK

The medications administered to patients with TAK are shown in Figure 3a. Approximately half of the patients used an immunosuppressive agent. Immunosuppressive agents other than MTX and CsA, including azathioprine (AZA), cyclophosphamide (CY) and tacrolimus were used in seven cases, and biologic agents were used in four patients (tocilizumab in two, infliximab in one and adalimumab in one).

Surgical interventions in patients with TAK

During the follow-up period, surgical interventions were required for 32 patients with TAK. The most common operation was aortic root replacement (ARR) together with aortic valve replacement (AVR) for aortic root dilatation with AR (Fig. 3b). ARR alone, AVR alone, percutaneous transluminal renal angioplasty (PTRA) or arterial bypass operations were performed in certain cases. The cumulative incidence curve showed that the peaks of those operations were during the initial 2 years and approximately 5 years after diagnosis.

Comparison of treatment and prognosis between early- and late-onset patients with TAK

Although patients with late-onset TAK tended to use fewer immunosuppressive agents than those with early-onset TAK because of the risk of side effects, there were

Table 3 Comparison of the clinical characteristics between patients with early- and late-onset Takayasu arteritis

	Age at onset ≤ 40	Age at onset > 40	P
Cases, n	58	28	
Age at onset, years ± SD	24.9 ± 7.6	60.1 ± 9.9	< 0.001
Female, n (%)	55 (94.8%)	24 (85.7%)	0.21
CRP, mg/dL ± SD	4.9 ± 4.6	4.9 ± 3.6	0.99
ESR, mm/h ± SD	61.1 ± 47.5	73.4 ± 50.8	0.44
Hypertension, n (%)	17 (29.3%)	17 (60.7%)	0.009
Aortic regurgitation, n (%)	29 (50%)	13 (46.4%)	0.82
Ischemic optic neuropathy, n (%)	1 (1.7%)	1 (3.6%)	0.55

The values of age at onset, CRP, and ESR indicate mean ± SD. *P*-values were determined by comparison between the two groups. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
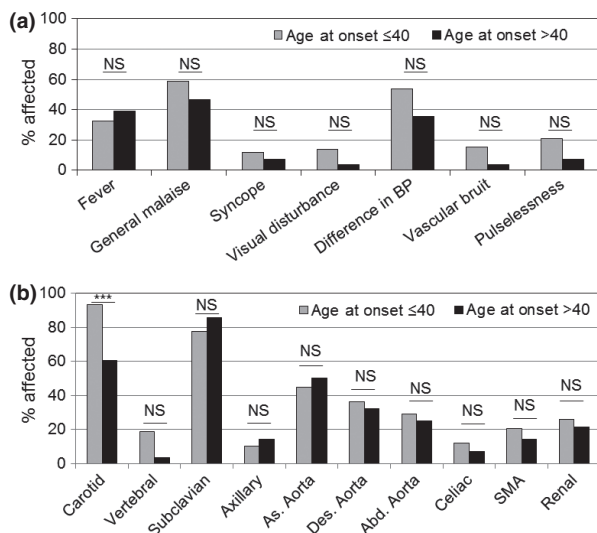

Figure 2 (a) Symptoms and physical findings at diagnosis in patients with early- and late-onset TAK. (b) Distribution of arterial involvement in patients with early- and late-onset TAK. As. Aorta, ascending aorta; Abd. Aorta, abdominal aorta; BP, blood pressure; Des. Aorta, descending aorta; NS, not significant; SMA, superior mesenteric artery; TAK, Takayasu arteritis. ***P < 0.001.

no statistically significant differences in the medications and surgical interventions used between patients with early- and late-onset TAK (Fig. 4a,b). The survival rate of patients with late-onset TAK was also comparable with that of patients with early-onset TAK (Fig. 5).

DISCUSSION

In the present study, we retrospectively analyzed the clinical characteristics and outcomes of 95 patients with LVV. Study results demonstrated that patients with TAK had a higher prevalence of AR and a higher rate of carotid and subclavian arterial involvement but had a better prognosis than those with GCA. Our study results also suggested that the clinical characteristics, distribution of arterial lesions, treatments administered and prognoses of patients with early- and late-onset TAK were comparable.

As expected, patients with GCA had a significantly higher age at onset, a higher rate of PMR, and a worse prognosis compared with those with TAK in our study. Aortic involvement was observed in four of nine patients (44.4%) with GCA. Maksimowicz-McKinnon et al.[5] reported that the frequency of aortic involvement in patients with GCA was 62% and that the distribution of arterial involvement showed strong similarities between patients with TAK and GCA; however, they also demonstrated that patients with TAK were more likely to have carotid, subclavian and iliac artery disease than those with GCA. These results were consistent with those obtained in our study.

AR was not observed in patients with GCA in our study (Table 1). Nuenninghoff et al.[17] reported that aortic insufficiency murmur was observed in only four of 168 (2.4%) patients with GCA. Costello et al.[18] also suggested that AR was a rare but severe complication of GCA. The relatively higher frequency of ascending aortic involvement in patients with TAK may be associated with differences in the rate of AR observed between the two groups (Fig. 1c).

The most significant prognostic factors for TAK are considered to be the presence of AR, renal arterial stenosis, aortic coarctation and aneurysms; however, the prognosis for patients with TAK has improving in recent years for unknown reasons.[3,13] In contrast, the most common causes of death in GCA were
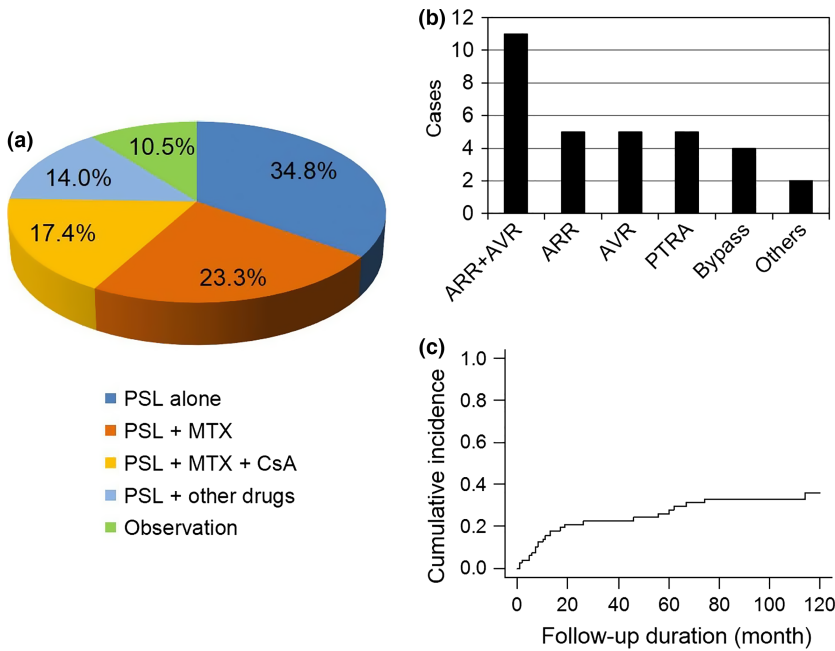
Figure 3 (a) Medications administered to patients with TAK. (b) Surgical interventions performed in patients with TAK. (c) The cumulative incidence curve of surgical interventions in patients with TAK. ARR, aortic root replacement; AVR, aortic valve replacement; CsA, cyclosporine A; MTX, methotrexate; PTRA, percutaneous transluminal renal angioplasty; PSL, prednisolone; TAK, Takayasu arteritis.
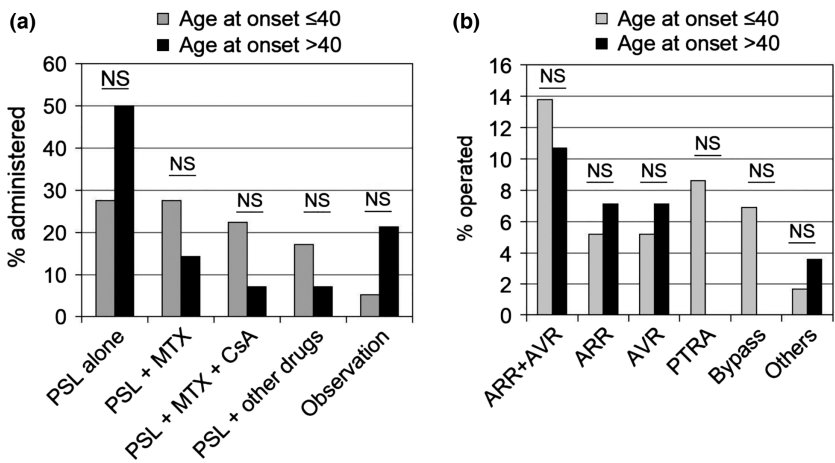

Figure 4 (a) Medication administered to patients with early- and late-onset TAK. (b) Surgical interventions in patients with early- and late-onset TAK. ARR, aortic root replacement; AVR, aortic valve replacement; CsA, cyclosporine A; MTX, methotrexate; NS, not significant; PTRA, percutaneous transluminal renal angioplasty; PSL, prednisolone; TAK, Takayasu arteritis.

malignancies, infections and geromarasmus.[13] Although patients with TAK had a significantly higher prevalence of AR than those with GCA, differences in the survival rates between the two groups may have been attributable to differences in the age at onset. Collectively, our study results suggested that TAK and GCA showed not only similarities but also substantial differences, such as carotid and subclavian arterial involvement, the rate of AR and PMR, and prognosis in Japanese patients with TAK and GCA.

Because there are no placebo-controlled, randomized clinical trials on the subject, the level of evidence for the appropriate medical management of TAK is low.[19]

The most commonly used agents include corticosteroids and conventional immunosuppressive agents, such as MTX, AZA, CY, CsA and mycophenolate mofetil.[19] In the present study, the most prescribed immunosuppressive agent was MTX, followed by CsA. Recently, the use of biologic agents has been increasing worldwide.[20] The therapeutic effects attributed to anti-tumor necrosis factor inhibitors (infliximab, adalimumab and others), an anti-CD20 monoclonal antibody (i.e., rituximab) and an anti-interleukin 6 receptor antibody (i.e., tocilizumab) seem to be promising.[20] Therefore, the use of biologic agents for patients with TAK will increase in our department.
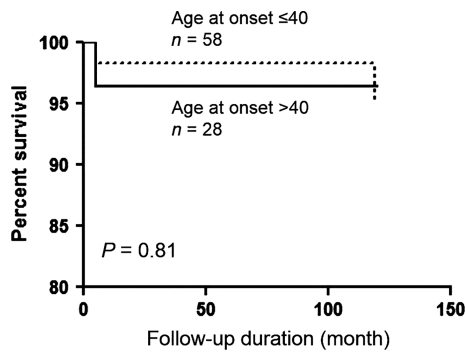
Figure 5 Survival curves in patients with early- and late-onset Takayasu arteritis.

Surgical interventions remain important for the treatment of stenosed or occluded arteries, aneurysmal lesions and severe AR. Serological inflammation at the time of operation is strongly associated with the occurrence of complications after vascular procedures.[21] In the present study, the median durations from diagnosis to operation were 51, 13 and 34 months for cardiac or aortic root surgery (ARR and AVR), PTRA and arterial bypass surgery, respectively. These results indicated that highly invasive surgeries, such as ARR and AVR, were performed in an absolutely quiescent stage of the disease.

In the present study, the clinical characteristics, symptoms and physical findings at diagnosis, distribution of arterial lesions, treatments administered and prognoses of patients with early- and late-onset TAK were comparable, with the exceptions of the frequencies of hypertension and carotid arterial involvement. The observed differences in the frequency of hypertension were likely attributable to essential hypertension in patients with late-onset TAK, as the rate of renal arterial involvement was comparable between the two groups (Fig. 2b). Furthermore, although all patients with early-onset TAK met the 1990 ACR criteria, approximately 60% of patients with late-onset TAK did not fulfill the ACR criteria due to the age restriction in the present study. These results suggested that the ACR criteria was unsuitable for the diagnosis of patients with late-onset TAK, and that the age restriction for disease onset (≤ 40 years) may not be essential to the diagnosis of TAK, as previously noted.[9,10] To overcome these challenges, a global project referred to as the Diagnostic and Classification in Vasculitis Study is underway to form new classification criteria for all vasculitides.[22]

Although TAK was first reported in 1908 by the Japanese ophthalmologist Mikito Takayasu as a case of

peculiar changes in the central retinal vessels,[23] the frequency of ION was rare (3.4%) in our patients with TAK. The typical arteriovenous anastomosis around the optic disc reported by Takayasu is now considered to be a late-stage finding.[24] The reported frequency of ION may be decreasing due to recent advances in imaging modalities, such as enhanced CT, MRA and FDG-PET, which allow for earlier and more accurate diagnosis of TAK.[25]

The present study had several limitations. First, the design of our study was retrospective. Further prospective studies will be required to confirm our findings. Second, although the number of patients with TAK enrolled in the present study was relatively large, the size of the GCA group was small. This may reflect racial differences in the prevalence of GCA, as it is extremely rare in Asian countries.[26] Third, we did not assess TAK or GCA disease activity. Recently, the Indian Takayasu Clinical Activity Score has been proposed for the evaluation of TAK disease activity.[27] In addition, it has been reported that serum pentraxin-3 levels can predict the progression of arterial lesions in patients with TAK; however, we did not assess this novel clinical score or biomarker.[28] Therefore, Figure 3a merely represents the medications administered to patients with TAK at a single point irrespective of disease activity. Fourth, because the frequency of headache varies from 70% to 85% in GCA, differences in the rate of carotid arterial involvement between patients with early- and late-onset TAK may represent the possibility that patients who did not fulfill the criteria of GCA due to a lack of headaches and temporal arterial abnormalities were included in the group of patients with late-onset TAK (Fig. 2b). GCA without cranial involvement may be labelled as large-vessel GCA in other centers.[29] A previous report suggested that large-vessel GCA presented earlier than cranial GCA, and median age at onset was 66 and 72 years, respectively.[29] Therefore, the late-onset TAK group in our study may be labelled as large-vessel GCA. However, these patients do not fulfill the classification criteria of GCA, suggesting that it is extremely difficult to differentiate late-onset TAK from GCA without cranial arterial involvement.

In conclusion, we demonstrated that Japanese patients with TAK or GCA shared similarities regarding the distribution of arterial involvement; however, substantial differences, such as the prevalence of AR and PMR, carotid and subclavian arterial involvement, and patient prognoses, were also found to exist. Our study results also showed that the clinical characteristics, arterial involvement, treatments administered and the prog-

noses of patients with early- and late-onset TAK were comparable. These results suggested that the age restriction for disease onset (≤ 40 years) may not be necessary for the diagnosis of TAK.

CONFLICT OF INTEREST

None.

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