Gender differences in clinical and angiographic findings of patients with Takayasu arteritis

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ABSTRACT

Objective. *Because Takayasu arteritis (TA) predominantly affects females, few data regarding gender differences have been reported. The aim of the present study is to describe clinical features and angiographic findings of patients with TA according to gender.*

Methods. *According to the 1990 American College of Rheumatology criteria, 294 patients were diagnosed with TA between September 1994 and April 2014 at a single tertiary hospital. We reviewed clinical, laboratory, and radiologic data at the time of diagnosis.*

Results. *Among the 294 patients studied, 257 (87.4%) were female (male:female ratio=1:6.9). Female patients had a higher tendency to exhibit blood pressure differences between arms (p=0.595) and a weak pulse at the brachial artery (p=0.063). In male patients, we observed higher serum creatinine levels (p=0.038) and hypertension more frequently (p=0.061) than in females. Females exhibited more common lesions in the thoracic aorta and its branches, while males had more frequent lesions in the abdominal aorta and its branches. An analysis of angiographic classification according to the International TA Conference in Tokyo 1994 classification revealed that male patients had a higher incidence of type IV and females showed a higher incidence of types I, IIa, and IIb.*

Conclusion. *Female patients with TA have more frequent involvement of the thoracic aorta and its branches, whereas involvement of the abdominal aorta and its branches is more common in males. Considering these gender-specific differences, adjustment of diagnostic criteria for TA according to gender may be necessary.*

Introduction

Takayasu arteritis (TA) is a rare inflammatory disorder primarily involving the aorta and its main branches (1). Granulomatous inflammation in the adventitia and medial wall of the artery causes diffuse wall thickening, luminal narrowing, occlusion, and dilatation at the site of the lesion (2, 3). The clinical presentation of TA includes systemic inflammatory symptoms such as fever, fatigue, arthralgia, weight loss, and vascular complications according to the distribution the involved vessels such as visual disturbance, claudication, weak pulse, differences in blood pressure between arms, hypertension, and stroke (4, 5).

TA is predominantly observed in females though, male to female ratios vary by country (6). Although there have been many epidemiologic studies of TA, few data have identified gender differences as well as clinical features of male patients with TA. Even though Sharma *et al*. and Mont'Alverne *et al*. described features of TA in both genders, these studies did not sufficiently identify gender-specific differences due to the relatively small numbers of patients studied, and their results were conflicting (7, 8). Thus, the aim of present study was to describe clinical features and angiographic findings between male and female in one of the largest cohort. We also investigated whether gender differences in TA were related to known ethnic differences.

Methods

Study population

We identified all patients who were diagnosed with TA between September 1994 and April 2014 at a single tertiary medical centrr in Seoul, Korea. Two hundred and ninety-four patients who satisfied the the 1990 American College of Rheumatology (ACR) diagnostic criteria were included (9). Their median follow-up duration was 63.7 months.

Data collection

We retrospectively reviewed clinical, laboratory and angiographic findings

from medical records of all patients. Clinical information included comorbid disease and patients' signs and symptoms at the time of diagnosis. Comorbidities were comprised of diabetes mellitus, hypertension, dyslipidaemia, chronic kidney disease (CKD), stroke, tuberculosis, angina, and congestive heart failure. Patients were regarded as having diabetes mellitus, hypertension, and dyslipidaemia if they carried a previous diagnosis, were prescribed medicine for the condition, or had a fasting glucose ≥126 mg/dl, a random blood pressure ≥140/90 mmHg, and a total cholesterol >200 mg/dl or low density lipoprotein (LDL) cholesterol >130 mg/dl, respectively. In evaluating hypertensive patients, we excluded patients whose true blood pressure was unknown because of disease involvement. CKD was defined as a serum creatinine >2.0 mg/dl or a previous diagnosis of CKD. Current smokers and ex-smokers were included in the smoking group. Similarly, patients were classified as having stroke, tuberculosis, or angina if they were previously diagnosed with or taking medications to treat these conditions. Additionally, patients were classified as having congestive heart failure if they had current signs and symptoms related to heart failure such as pulmonary oedema or carried a previous diagnosis

We collected data on patients' signs and symptoms of disease as well as available laboratory data including CBC, erythrocyte sedimentation rate (ESR), high sensitivity-C reactive protein (hs-CRP), blood urea nitrogen (BUN), serum creatinine, N-terminal pro-brain natriuretic peptide (NT-proBNP), lipoprotein(a) (Lp(a)), and homocysteine level at the time of diagnosis. Of the patients without laboratory data at the time of diagnosis, we obtained the closest values to the time of diagnosis. The level of NT-proBNP in patients with a serum creatinine more than 2.0 mg/dl was not analysed because of decreased renal excretion.

For vascular evaluation, we reviewed various imaging modalities including duplex ultrasonography, CT angiography, MR angiography and conventional angiography. Of 294 patients with TA, 5 patients (1.7%) did not undergo systemic angiographic evaluation and 188 patients (63.9%) did not undergo coronary evaluation. Of the 5 patients without systemic angiographic evaluation, 4 patients had evaluation of the carotid arteries via duplex scan or CT angiography and 1 patient was diagnosed via CT angiography of the abdominal aorta and arteries of the lower extremities. All 5 patients were excluded in the evaluation of angiographic type. The angiographic type was determined by the International TA Conference in Tokyo 1994 angiographic classification (10). And active TA was defined as having at least one of following: i) ESR >20 mm/h and CRP >1.0 mg/dl, ii) carotidynia, and iii) erythema nodosum.

This study was approved by the institutional review board of Samsung Medical Centre.

Statistical analysis

We analysed the clinical and angiographic findings of male and female patients using chi square and Fisher's exact tests as appropriate. For laboratory findings, continuous variables were shown as mean ± one standard deviation or median and interquartile range (IQR). Independent *t*-tests were used for comparisons between genders. All tests were two sided, and *p*-values less than 0.05 were considered to be statistically significant. SPSS version 21 was used for all statistical analyses.

Results

Clinical characteristics

Among the 294 patients with TA, 257 (87.4%) were female with a male to female ratio of 1:6.9. The mean age at the time of the onset of symptoms was 28.4±13.3 years in males and 32.0±13.0 years in females (p=0.135). Twenty-eight patients (9.5%) were asymptomatic and diagnosed incidentally. Sixty-three patients (21.4%) had onset of symptom after 40 years of age. Comorbid disease and clinical features in patients with TA are shown in Table I. Hypertension was the most common (195 patients, 69.1%) and other comorbidities were as follows; dyslipidaemia (107 patients, 36.9%), angina (59 patients, 20.1%), and tuberculosis (47 patients, 17.6%). Male patients had a tendency towards a higher incidence of hypertension (82.9% *vs*. 67.2%, p=0.061). However, there was no significant difference in comorbidities between genders with the exception of smoking, which was significantly higher in males than in females (50.0% *vs*. 4.8%, p<0.001).

The frequent signs or symptoms in patients with TA included bruit on auscultation over the subclavian arteries or abdominal aorta (234 patients, 80.1%), weak pulse at the brachial arteries (211 patients, 72.3%), differences in blood pressure between arms >10 mmHg (178 patients, 60.8%), dizziness (109 patients, 37.1%), and claudication (107 patients, 36.4 %). Constitutional symptoms including subjective fever, sweating, fatigue, malaise, weight loss, and arthralgia were present in 52 patients (17.7%). Erythema nodosum and carotidynia as presenting symptoms of active TA were relatively less common in 5 patients (1.7%) and 22 patients (7.5%), respectively. In female patients, bruits were significantly more common (65.7% *vs*. 82.1%, p=0.023) than in males. Also, female patients showed a trend towards a higher incidence of weak pulse at the brachial arteries (59.5% *vs*. 74.1%, p=0.063), differences in blood pressure between arms >10 mmHg (56.8% *vs*. 61.3%, p=0.595), visual dimness (8.1% *vs*. 14.8%, p=0.273), and dizziness (29.7% *vs*. 38.1%, p=0.322), which could be related to the involvement of the aortic arch and its branches.

Baseline laboratory findings for all patients are shown in Table II. Female patients had significantly lower haemoglobin levels (median [IQR]: 14.4 g/dl [12.8–15.5 g/dl] *vs*. 12.2 g/dl [11.1-13.1 g/dl]; p<0.001) than males. CRP levels were similar (0.19 mg/dl [0.07–0.99 mg/dl] *vs*. 0.22 mg/dl [0.06–1.12 mg/dl]; p=0.629) between groups and the serum creatinine was significantly higher (0.97 mg/dl [0.84–1.10 mg/dl] *vs*. 0.76 mg/dl [0.66–0.81 mg/dl]; p=0.038) in male patients than in females. No significant differences were observed in levels of NT-proBNP, Lp(a) or homocysteine.

With respect to disease activity, there were no statistically significant differ-

Table I. Comorbidities and clinical features according to gender.

	Male (%) n=37	Female (%) n=257	*p*-value
Co-morbidity			
Diabetes mellitus	1/37 (2.7)	13/257 (5.1)	1.000
Hypertension	29/35 (82.9)	166/247 (67.2)	0.061
Dyslipidaemia	15/37 (40.5)	92/253 (36.4)	0.623
Smoking	18/36 (50.0)	12/252 (4.8)	<0.001
Chronic kidney disease	2/37 (5.4)	8/254 (3.1)	0.370
Stroke	1/37 (2.7)	23/256 (9.0)	0.333
Tuberculosis	7/33 (21.2)	40/234 (17.1)	0.561
Angina	9/37 (24.3)	50/257 (19.5)	0.489
Congestive heart failure	5/37 (13.5)	26/257 (10.1)	0.565
Signs & symptoms			
Constitutional symptom	7/37 (18.9)	45/263 (17.5)	0.834
Fever	0/37 (0.0)	9/257 (3.5)	0.609
Arthralgia	0/37 (0.0)	12/257 (4.7)	0.374
Weight loss	3/37 (8.1)	10/257 (3.9)	0.216
Erythema nodosum	0/37 (0.0)	5/257 (1.9)	1.000
Carotidynia	2/37 (5.4)	20/257 (7.8)	1.000
Headache	8/37 (21.6)	59/257 (23.0)	0.856
Dizziness	11/37 (29.7)	98/257 (38.1)	0.322
Visual dimness	3/37 (8.1)	38/257 (14.8)	0.273
Dyspnea on exertion	6/37 (16.2)	74/257 (28.8)	0.108
Claudication	17/37 (45.9)	90/257 (35.0)	0.197
Upper limb claudication	3/37 (8.1%)	41/257 (16.0%)	0.211
Lower limb claudication	14/27 (37.8%)	49/257 (19.1%)	0.009
Bruit	23/35 (65.7)	211/257 (82.1)	0.023
Blood pressure difference between arms >10 mmHg	21/37 (56.8)	157/256 (61.3)	0.595
Weak pulse at the brachial arteries	22/37 (59.5)	189/255 (74.1)	0.063

Table II. Baseline laboratory findings in TA patients.

	Male Median (IQR)	n.	Female Median (IQR)	n.	*p*-value
WBC (/ul)	6700.0 (5450.0-9140.0)	37	6800.0 (5475.0-8485.0)	253	0.860
Haemoglobin (g/dl)	14.4 (12.8-15.5)	37	12.2 (11.1-13.1)	253	<0.001
ESR (mm/h)	13.0 (6.5-29.0)	37	28.0 (14.0-51.0)	252	0.005
CRP (mg/dl)	0.19 (0.07-0.99)	37	0.22 (0.06-1.12)	251	0.629
BUN (mg/dl)	13.7 (10.8-18.6)	37	12.3 (9.6-16.7)	252	0.543
Creatinine (mg/dl)	0.97 (0.84-1.10)	37	0.76 (0.66-0.81)	252	0.038
NT-proBNP (pg/ml)	54.0 (29.8-127.5)	24	122.6 (45.0-426.8)	183	0.577
Lp(a) (mg/dl)	18.8 (13.6-44.4)	27	26.1 (14.3-42.5)	152	0.880
Homocysteine (mg/dl)	12.4 (9.8-15.5)	26	9.9 (8.2-12.2)	151	0.197

IQR (Interquartile range).

ences between genders in erythema nodosum (0.0% *vs*. 1.9%, *p*=1.000), carotidynia (5.4% *vs*. 7.8%, *p*=1.000), or elevated ESR and CRP (18.9% *vs*. 26.8%, *p*=0.306) (Table III). However, positive disease activity (*i.e*. any one of the above three criteria) showed a higher tendency in female compared with male patients (21.6% *vs*. 30.8%, *p*=0.254).

Angiographic findings

In the distribution of angiographic findings in patients with TA (Table IV), the most common lesions were found in the main branches of the aortic arch: left common carotid artery (215 patients, 73.4%), left subclavian artery (192 patients, 65.8%), and right common carotid artery (187 patients, 63.8%). Female patients had more frequent involvement of the arteries in the thoracic cavity which included the ascending aorta (27.8% *vs*. 48.6%, *p*=0.019), arch (8.3% *vs*. 38.4%, *p*<0.001), descending thoracic aorta (27.8% *vs*. 59.7%, *p*<0.001), right common carotid artery (43.2% *vs*. 66.8%, *p*=0.005), left subclavian artery (45.9% *vs*. 68.6%, *p*=0.007), and left common carotid artery (45.9% *vs*. 77.3%, *p*<0.001).

On the other hand, male patients more commonly had lesions in the abdominal cavity: right renal artery (43.2% *vs*. 27.3%, *p*=0.046), right iliac artery (24.3% *vs*. 12.4%, *p*=0.049), and left iliac artery (29.7% *vs*. 10.0%, *p*=0.002). Although it was not statistically significant, male patients tended to exhibit more prominent involvement of other abdominal arterial branches (celiac artery, superior mesenteric artery, inferior mesenteric artery, and left renal artery). Males and females were similar with respect to the incidence of atypical coarctation (18.9% *vs*. 19.3%, *p*=0.957), involvement of the coronary arteries (56.3% *vs*. 51.1%, *p*=0.705), and involvement of the pulmonary arteries (5.6% *vs*. 11.1%, *p*=0.396). Among the 195 patients with hypertension, 84 patients (43.1%) had renal artery involvement and 49 patients (25.1%) had atypical coarctation.

The distribution of angiographic types according to gender is shown in Fig. ure 1. Among the patients with TA, the most common angiographic type was type V (152 patients, 50.9%). Male patients showed a higher incidence of type IV (18.9% *vs*. 4.4%), which involved the abdominal aorta and its main branches. Female patients, on the other hand, had a higher incidence of types which involved the aorta within the thoracic cavity such as type I (13.5% *vs*. 17.1%), type IIa (5.4% *vs*. 8.3%), and type IIb (8.1% *vs*. 15.1%) compared with male patients.

We compared the distribution of angiographic types in patients with TA in our study to that of other countries (Fig. 2). Including our data of which male to female ratio was 1:6.8, the gender ratios varied for each country from 1:1.7 to 25.7. In India and Thailand there was a high male to female ratio, and a tendency toward a higher incidence of type IV and lower incidence of types I and IIa. In contrast, there was a lower incidence of type IV and higher incidence of types I and IIa in Turkey and Japan in which male to female ratio was low.

Table III. Disease activity in TA patients.

	Male (%)	Female (%)	*p*-value
Erythema nodosum	0/37 (0.0)	5/257 (1.9)	1.000
Carotidynia	2/37 (5.4)	20/257 (7.8)	1.000
Elevated ESR & CRP	7/37 (18.9)	67/250 (26.8)	0.306
Disease activity (any one of the above)	8/37 (21.6)	77/250 (30.8)	0.254

Table IV. Comparison of angiographic findings in TA patients according to gender.

Site of involvement	Male (%) n=37	Female (%) n=257	*p*-value
Ascending aorta	10/36 (27.8)	123/253 (48.6)	0.019
Aortic arch	3/36 (8.3)	98/255 (38.4)	<0.001
Descending thoracic aorta	10/36 (27.8)	151/253 (59.7)	<0.001
Abdominal aorta	23/37 (62.2)	151/254 (59.4)	0.753
Atypical coarctation	7/37 (18.9)	49/254 (19.3)	0.957
Right innominate artery	16/37 (43.2)	106/254 (41.7)	0.862
Right subclavian artery	16/37 (43.2)	141/256 (55.1)	0.177
Right common carotid artery	16/37 (43.2)	171/256 (66.8)	0.005
Right internal carotid artery	8/37 (21.6)	68/256 (26.6)	0.522
Right external carotid artery	1/37 (2.7)	20/256 (7.8)	0.260
Left subclavian artery	17/37 (45.9)	175/255 (68.6)	0.007
Left common carotid artery	17/37 (45.9)	198/256 (77.3)	<0.001
Left internal carotid artery	9/37 (24.3)	71/256 (27.7)	0.663
Left external carotid artery	4/37 (10.8)	29/256 (11.3)	1.000
Celiac artery	10/37 (27.0)	50/253 (19.8)	0.308
Superior mesenteric artery	12/37 (32.4)	51/253 (20.2)	0.091
Inferior mesenteric artery	2/37 (5.4)	8/253 (3.2)	0.622
Right renal artery	16/37 (43.2)	69/253 (27.3)	0.046
Left renal artery	14/37 (37.8)	69/253 (27.3)	0.184
Right iliac artery	9/37 (24.3)	31/251 (12.4)	0.049
Left iliac artery	11/37 (29.7)	25/251 (10.0)	0.002
Coronary artery	9/16 (56.3)	46/90 (51.1)	0.705
Pulmonary artery	2/36 (5.6)	28/253 (11.1)	0.396

Discussion

Our study identified the clinical characteristics and angiographic findings in the majority of patients with TA in Korea, and also evaluated gender-specific differences between them. In the patients with TA, the main branches of the aortic arch were the most common lesion sites. Female patients had more frequent involvement of the thoracic aorta and its branches, whereas involvement of the abdominal aorta and its branches were more common in males.

The differences of angiographic findings between males and females also corresponded with their clinical features. Female patients had more prominent features in dizziness, visual dimness, weak pulse at the brachial arteries, and differences in blood pressure between arms >10 mmHg, which may relate to lesions of the aortic arch and its branches. On the other hand, hypertension and elevated serum creatinine may be caused by lesions within the abdominal cavity, which were more prevalent in male patients.

The present study showed that active TA was more common in female patients, though this was not statistically significant but was similar to that observed in other studies (11, 12). The appropriate criteria for disease activity of TA have been controversial and challenging. Because there are no distinct criteria which have been validated and standardized in TA, the National Institutes of Health (NIH) criteria for disease activity are commonly used (1). However, it is difficult to assess disease activity by the NIH criteria at the time of diagnosis without follow-up data. Recently, Misra *et al*. suggested the Indian Takayasu Clinical Activity Score (ITAS2010) for clinical disease activity (13). However, this was not suitable for use in our study because it is still in the process of being validated and edited. Additionally it needs much information for scoring, which may not available in a retrospective study. Therefore, we classified patients with active TA according to simplified criteria including increased ESR and CRP, carotidynia, and erythema nodosum at the time of diagnosis except follow up data such as tissue confirmation or disease progression, because whether TA was active state or not at the time of diagnosis were critical to make a treatment plan. Though we adopted these criteria in our study, further investigation to assess disease activity of TA will be needed.

With regard to gender differences in angiographic findings, we showed that the distribution of angiographic type of which males had a higher incidence of type IV, though females were primarily type I and II in patients with TA. Figure 2 shows similar findings based on different gender ratios observed in other cohorts (10, 14-16). Until now, most studies have explained that this difference in the distribution of lesions is caused by geographic or ethnic differences (5, 6, 10, 11, 14). However, Fig. 2 shows that as the male to female ratio increases, the frequency of abdominal aortic lesions increases. Additionally, as the ratio of female patients increases, the incidence of type I and II involving mainly the thoracic aorta and its branches increases. We suggest that the gender ratio rather than ethnic differences result in different angiographic findings in TA, and could also possibly explain the geographic difference as well.

Our findings are consistent with the results reported by Sharma *et al*., who showed that Indian male patients with TA more commonly had involvement of the abdominal aorta and its branches, and female patients had a tendency towards more frequent aortic arch lesions (7). However, they did not show statistical significance due to the relatively small number of patients studied with the exception of more common involvement of the left renal artery in male patients. Moreover, these findings were substantially different from those of Mont'Alverne *et al*. who found that ascending aortic aneurysms were more common in male patients with TA in Brazil, and female had a trend towards more frequent stenosis or occlusion in

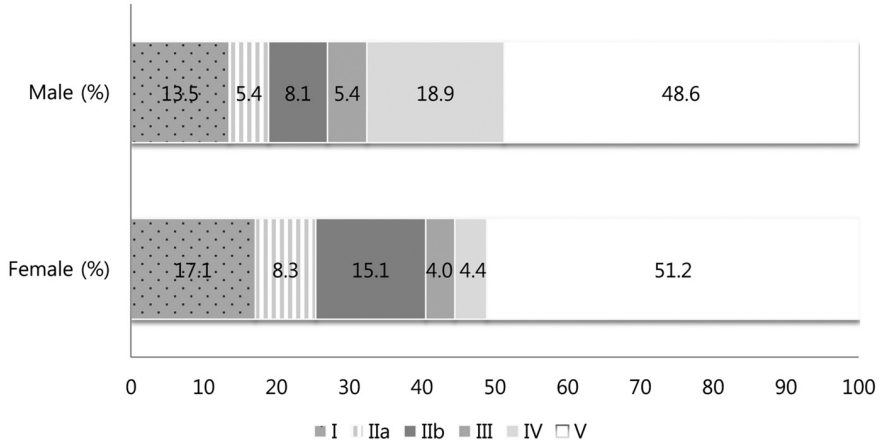

Fig. 1. Distribution of angiographic type according to the International Takayasu Arteritis Conference in Tokyo 1994 classification between male and female patients with TA.

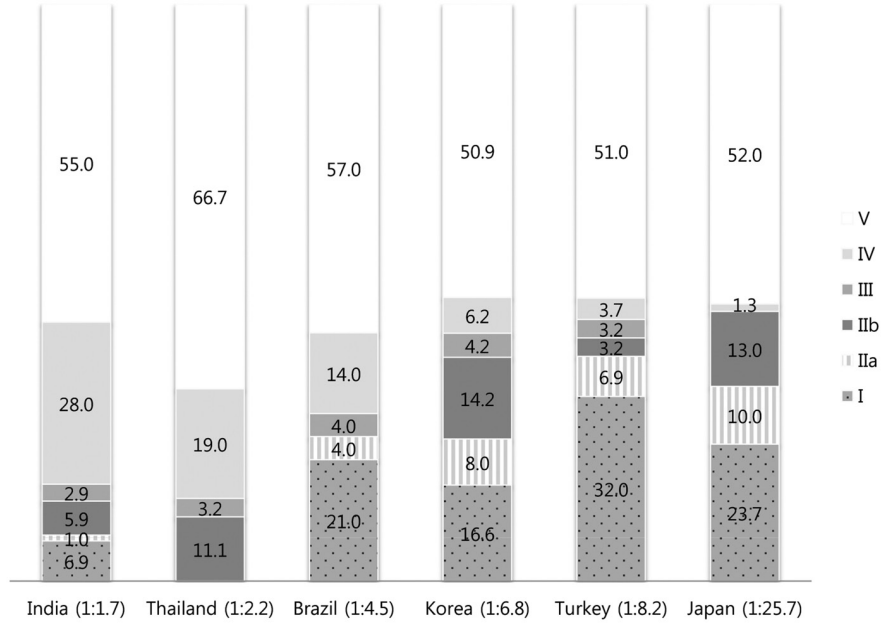

Fig. 2. Distribution of patients with TA according to angiographic type for each country. The angiographic type is determined by the International Takayasu Arteritis Conference in Tokyo 1994 classification. Numbers inside the bars represent the percentage of patients with TA for each type of angiographic classification and numbers by the side of country name below the graph refer to male to female ratios.

the abdominal aorta (8). Therefore, we propose gender-specific differences in angioraphic findings based on a large number of patients with TA that included frequent lesions of the thoracic aorta and its branches in females and of the abdominal aorta and its branches in males.

However, there has been no study to date regarding why gender difference in TA occurs. Many autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and thyroiditis exhibit female predominance as well as TA. In the cases of autoimmune disease, because of the influence of sex hormones, clinical features are differentially manifested between males and females (17, 18). Moreover, studies of which sex chromosome complement affects female biased autoimmunity have emerged (19, 20). It appears that multiple factors such as various genetic susceptibilities and sex hormones contribute to the gender difference in TA, which is similar to other autoimmune disorders (4, 21, 22). Interestingly, although fibromuscular dysplasia is a non-inflammatory disease, Esther *et al*. showed that male patients with fibromuscular dysplasia had higher rates of renal and mesenteric artery involvement, whereas female patients had more common involvement of the extracranial carotid and vertebral arteries (23), which was similar to our findings. With regard to determining the causes of these gender-specific characteristics, further studies are needed.

We demonstrated that male patients with TA primarily had involvement of arteries in the abdominal cavity. Accordingly, male patients often did not satisfy the ACR criteria for TA such as decreased brachial artery pulses and blood pressure differences between arms >10 mmHg. At our institution, there were several male patients who did not fulfill 3 or more ACR criteria and were excluded from this study. However, they have been managed in accordance with recommended treatment for TA. Because current diagnostic criteria are comprised of findings more common in females, modification of these criteria according to gender may be required.

Present study has several limitations. Because of its retrospective design, we were able to collect limited data from medical records. Since our data were based not on follow-up progress but those at the time of diagnosis, we could minimise missing data that might be noticed in the process of follow-up. In addition, our study population was obtained from a single tertiary referral centre, thus there could be a selection bias. However, our case numbers could be enough to represent TA patients in Korea.

In summary, we identified clinical features and angiographic findings of male and female patients with TA. Female patients with TA more commonly exhibited involvement of the aorta and its branches within the thoracic cavity, whereas male patients had more frequent involvement of the abdominal aorta and its branches. Therefore, this difference might be considered for adjustment of diagnostic criteria of TA according to gender. Future investigations will be necessary to identify the aetiology of this gender difference.

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