ORIGINAL PAPER

Comparison of clinicodemographic characteristics and pattern of vascular involvement in 126 patients with Takayasu arteritis: a report from Iran and Turkey

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SUMMARY

Takayasu arteritis (TA) is an extremely uncommon vasculitis that primarily affects the aorta and its branches. Due to the genetic and ethnicity effect, a diverse array of TA clinical manifestations has been reported worldwide. The purpose of the present study was to compare the clinicodemographic characteristics and pattern of vascular involvement of Iranian and Turkish TA patients.

This study was a retrospective, cross-sectional investigation of 126 TA patients in Iran and Turkey. All of the variables analyzed were extracted from historical medical records.

In 126 TA patients, the ratio of females to males was 8.6:1, and the average age at onset of disease was 30.5±11.1 years. Fatigue (49.2%) and a weak or absent pulse (79.4%) were the most prevalent symptoms and signs, respectively. The most prevalent angiographic classifications were types V and I in Iranian patients (41.09%) and type I in the Turkish population (47.7%) The left subclavian artery was the vessel most frequently affected by TA (66.6%).

Our findings indicated that there were no significant differences between the two countries in terms of clinicodemographic characteristics or vascular involvement. Some clinical manifestations, such as claudication, were more prevalent in the Turkish population due to a higher incidence of occlusive lesions in the right subclavian artery.

Key words: *Takayasu arteritis, vasculitis, clinical characteristics, angiography classification.*

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INTRODUCTION

Takayasu arteritis (TA) is a rare vasculitis of large vessels that primarily affects the aorta and its major branches. TA is prevalent among females in their second and third decades and has a worldwide distribution. The reported prevalence of TA ranges from 0.9 per million in the United States (1) to 40 per million in Japan (2). The ratio of females to males also varies by country, ranging from 2.91:1 in China to 10:1 in Turkey (3-7). This disparity in reported data is likely attributable to the effect of ethnicity, the rarity of this disorder, and differences in study methodology (5).

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The clinical manifestations of this vasculitis of large vessels range from mild constitutional symptoms to severe manifestations due to vascular stenosis, occlusion, or aneurysm. In this category are myocardial infarction (MI), cerebrovascular accidents (CVA), intestinal and limb ischemia (5).
As previously stated, studies from various countries have reported a wide range of results regarding the clinicodemographic characteristics of their TA patients. This variation in the clinical presentation of TA is primarily attributable to the genetic and environmental bases of all autoimmune disorders. Consequently, it is hypothesized that comparing the clinicodemographic characteristics of this disorder between countries may help guiding future research toward the discovery of the pathogenesis of TA. The purpose of the present study is to gain a deeper understanding of this topic by comparing the clinicodemographic characteristics and pattern of vascular involvement of Iranian and Turkish TA patients from five university centers.

MATERIALS AND METHODS

Study population

This is a cross-sectional study conducted between 2013 and 2020 on 82 Iranian and 44 Turkish TA patients recruited from five university centers. Patients from four Iranian universities, including 57 cases from Tehran, 14 cases from Guilan, 8 cases from Kerman, and 3 cases from Qom University of Medical Sciences, were included in the study. Turkish patients were selected from hospitals affiliated with Uluda University in Bursa. All of the patients met the American College of Rheumatology's 1990 classification criteria for TA (8).

Demographic and clinical data

All variables, including age, gender, and disease duration, were extracted from the medical record of the patient. Due to the slow progression of TA, the disease was considered to have begun at the time of diagnosis. The duration of the disease was calculated from the disease's onset to March 2020. The clinical manifestations and examination findings were also reported at the time of diagnosis and initial presentation.

Vascular involvement pattern

Magnetic resonance angiography (MRA), computed tomography angiography (CTA), and conventional angiography were used to evaluate the vascular involvement (9-12). All patients underwent MRA or CTA for categorization of vascular involvement. Type I primarily affects aortic branches; type IIa the ascending aorta, aortic arch, and its branches; type IIb the ascending aorta, aortic arch, and its branches as well as descending thoracic aorta; Type III the descending thoracic aorta, abdominal aorta, and/or renal arteries; and type IV only affects coronary [C(+)] and pulmonary [P(+)] arteries, respectively (13).
Moreover, 82 patients underwent transthoracic echocardiography (TTE). Patients with a Doppler echocardiography-estimated systolic pulmonary arterial pressure (sPAP) of 40 mmHg or greater were considered to have pulmonary hypertension (PH) (14). Systolic dysfunction was described as a left ventricle ejection fraction (LVEF) of less than 50% on TTE (15). Grading of LV diastolic dysfunction according to American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) guidelines (16). Valvular stenosis and regurgitation were also assessed in accordance with EACVI and ASE guidelines (17).

Statistical analysis

The Shapiro-Wilk test was utilized to examine the normal distribution of variables in this study. Independent t-tests, chi-square tests, and Pearson's correlation tests were used to conduct analyses. A p-value of less than 0.05 was considered statistically significant. SPSS, version 22, was applied to perform statistical analyses for this study (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographic features

The current study included 126 TA patients: 82 from Iran and 44 from Turkey. The aver-

age age at disease onset was 30.5 years, 29.2±11.6 years in Iran, and 32.8±11.8 years in Turkey In the Iranian TA population, 85.3% of patients were female, resulting in a female-to-male ratio of 5.83:1. With a female-to-male ratio of 43:1, 97.7% of the Turkish population was female. Different ethnicities were present from the Iranian population, including 43 Persians (52.4%), 19 Turks (23.2%), 10 Kurds (12.2%), 5 Gilaks (6.1%), and one for Mazani, Arab, Turkoman, Afghan, and Ior (1.2%). In contrast, the entire Turkish TA population was of Turkic ethnicity.

Clinical manifestations

In terms of clinical symptoms, the most prevalent in the Iranian population was fatigue (54.9%), while it was claudication of the upper extremities in the Turkish population (68.2%). Weak or absent pulses were the most common finding at physical examination of the Iranian and Turkish populations, with a frequency of 80.5% and 77%, respectively. The comparison of clinical manifestations and laboratory data in the Iranian and Turkish populations is presented in Table I.

Pattern of vascular involvement and intervention

Type I and V were the most prevalent patterns among Iranian patients (each 41.0%), followed by type IIb (8.2%), IIa (5.4%), and IV (4.1%). Type III involvement was not found in the Iranian population. Type I

Table I - Clinical manifestation and laboratory data of Takayasu arteritis patients.

Variable	Total (N:126)	Iranian (N:82)	Turkish (N:44)	OR (CI 95%)	p-value
Constitutional/fatigue	63 (49.2%)	45 (54.9%)	17 (38.6%)	1.985 (0.939-4.197)	0.092
Weight loss	23 (18.3%)	19 (23.2%)	4 (9.1%)	3.065 (0.971-9.670)	0.055
Arthralgia	48 (38.1%)	33 (40.2%)	15 (34.1%)	1.329 (0.619-2.856)	0.564
Claudication-upper limb	68 (54.0%)	38 (46.3%)	30 (68.2%)	0.412 (0.191-0.891)	0.025
Claudication-lower limb	12 (9.5%)	5 (6.1%)	7 (15.9%)	0.348 (0.103-1.170)	0.111
Headache	44 (34.9%)	32 (39.0%)	12 (27.3%)	1.741 (0.783-3.872)	0.239
Syncope/falling	6 (4.8%)	5(6.01%)	1 (2.3%)	2.829 (0.320-25.010)	0.424
Dizziness/vertigo	29 (23.0%)	21 (25.6%)	8 (18.2%)	1.575 (0.632-3.925)	0.381
Palpitations	22 (17.5%)	19 (23.2%)	3 (6.8%)	4.188 (1.165-15.063)	0.026
Dyspnea	30 (23.8%)	26 (31.7%)	4 (9.1%)	4.727 (1.529-14.615)	0.004
Hemoptysis	5 (4.0%)	3 (3.7%)	2 (4.5%)	0.808 (0.130-5.025)	1.000
Carotidynia	15 (11.9%)	14 (17.1%)	1 (2.3%)	8.985 (1.140-70.821)	0.018
Hypertension	58 (46.0%)	33 (40.2%)	25 (56.8%)	0.523 (0.249-1.099)	0.094
Bruit	56 (44.4%)	35 (42.7%)	21 (47.7%)	0.543 (0.245-1.204)	0.162
Decreased or absent pulses	100 (79.4%)	66 (80.5%)	34 (77.3%)	1.165 (0.462-2.935)	0.813
Asymmetric blood pressure	77 (61.1%)	50 (61.0%)	27 (61.4%)	0.896 (0.413-1.943)	0.846
Cerebrovascular accident	7 (5.6%)	5 (6.1%)	2 (4.5%)	1.382 (0.257-7.432)	1.000
Myocardial infarction	5 (4.0%)	4 (4.9%)	1 (2.3%)	2.234 (0.242-20.626)	0.656
Thrombotic event	11 (8.7%)	9 (11.0%)	2 (4.5%)	2.662 (0.549-12.910)	0.325
Seizure	5 (4.0%)	5 (6.1%)	0 (0%)	0.938 (0.887-0.992)	0.161
Laboratory finding		**Total (N:126)**	**Turkish (N:44)**	**Iranian (N:82)**	**p-value**
WBC level*		9.2 (6.8-10.6)	9.2 (6.4-11.7)	9.2 (6.9-10.3)	0.339
Hb level*		11.9 (10.6-13.2)	11.6 (10-12.8)	12.2 (11.1-13.5)	0.436
ESR level*		39.4 (12.7-58)	41.1 (15-61.5)	38.4 (11.7-57.2)	0.382

OR, odds ratio; CI, confidence interval; WBC, white blood cell; Hb, hemoglobin; ESR, erythrocyte sedimentation rate. *Median (Q1-Q3).

Table II - Vascular involvement in Takayasu arteritis patients.

Variable	Total (N:126)	Iranian (N:82)	Turkish (N:44)	OR (CI 95%)	p-value	Missing N (%)
Left subclavian artery	84 (66.6%)	53 (77.9%)	31 (70.4%)	0.855 (0.382-1.914)	0.839	6 (4.8%)
Right subclavian artery	53 (42.0%)	39 (57.3%)	14 (31.8%)	2.143 (0.985-4.663)	0.059	6 (4.8%)
Left carotid artery	56 (44.4%)	37 (54.4%)	19 (43.1%)	1.248 (0.591-2.635)	0.575	6 (4.8%)
Right carotid artery	40 (31.7%)	28 (41.1%)	12 (27.2%)	1.469 (0.652-3.313)	0.421	6 (4.8%)
Vertebral artery	30 (23.8%)	19 (27.9%)	11 (25%)	1.000 (0.424-2.357)	1.000	6 (4.8%)
Ascending aorta	25 (19.8%)	21 (30.8%)	4 (9.0%)	3.818 (1.216-11.989)	0.019	6 (4.8%)
Aortic arch	27 (21.4%)	19 (27.9%)	8 (18.1%)	1.397 (0.551-3.543)	0.646	6 (4.8%)
Thoracic aorta	31 (24.6%)	23 (33.8%)	8 (18.1%)	1.783 (0.712-4.464)	0.271	8 (6.3%)
Abdominal aorta	31 (24.6%)	19 (38.7%)	12 (27.2%)	1.231 (0.517-2.930)	0.667	25 (19.8%)
Left renal artery	23 (18.2%)	16 (32%)	7 (15.9%)	2.063 (0.764-5.569)	0.162	25 (19.8%)
Right renal artery	22 (17.4%)	18 (36%)	4 (9.0%)	–	0.015	25 (19.8%)
Superior mesenteric artery	15 (11.9%)	13 (26.5%)	2 (4.5%)	–	0.012	25 (19.8%)
Inferior mesenteric artery	3 (2.3%)	3 (6.1%)	0 (0%)	0.946 (0.889-1.007)	0.119	26 (20.6%)
Celiac artery	16 (12.6%)	12(24.4%)	4 (9.0%)	2.667 (0.796-8.934)	0.168	25 (19.8%)
Left iliac artery	6 (4.7%)	5 (10.2%)	1 (2.2%)	4.135 (0.465-36.749)	0.171	25 (19.8%)
Right iliac artery	7 (5.5%)	6 (12.2%)	1 (2.2%)	5.059 (0.586-43.671)	0.105	25 (19.8%)
Coronary*	8	7 (26.9%)	1 (2.2%)	15.842 (1.820-137.883)	0.003	56 (44.4%)
Pulmonary°	8	5 (62.5%)	3 (6.8%)	22.778 (3.581-144.881)	0.001	74 (58.7%)

OR, odds ratio; CI, confidence interval. *Out of 26 in Iran and 44 in Turkey; °out of 8 in Iran and 44 in Turkey.

was the most prevalent pattern of vascular involvement in the Turkish population (47.7%), followed by type V (38.6%), type IIb (9.0%), type III (2.2%), and type IV (2.2%). In addition, there was one type IIa patient in the Turkish population. The most common vascular lesions among Iranian patients were stenosis (54.4%), increased wall thickness (18.1%), occlusion (15.2%), aneurysm (6.2%), and dilation (5.8%).

Table III - Angiographic classification in Takayasu arteritis patients.

Variable	Iranian (N:82)	Turkish (N:44)	p-value	OR (CI 95%)
Type I	30 (41.0%)	21 (47.7%)	0.472	–
Type IIa	4 (5.4%)	0 (0%)		
Type IIb	6 (8.2%)	4 (8.2%)		
Type III	0 (0%)	1 (2.2%)		
Type IV	3 (4.1%)	1 (2.2%)		
Type V	30 (41.0%)	17 (38.6%)		
C(+)*	7 (26.9%)	1 (2.2%)		
P(+)°	5 (62.5%)	3 (6.8%)		

OR, odds ratio; CI, confidence interval; C, coronary; P, pulmonary. *Out of 26 in Iran and 44 in Turkey; °out of 8 in Iran and 44 in Turkey.

Similarly, the most prevalent vascular lesions among Turkish patients were stenosis (44.4%), occlusion (26.1%), increased wall thickness (21.5%), aneurysm (4.5%), and dilation (3.2%).

The left subclavian artery was the most common vessel affected by TA in both Iranian and Turkish patients (77.9% *vs* 70.4%), followed by right subclavian artery (57.3%) and left common carotid artery (52.9%) in Iranian patients and left common carotid artery (43.1%) and right subclavian artery (31.8%) in Turkish patients (Tables II and III).

Except for the ascending aorta, superior mesenteric, coronary, and pulmonary arteries, which were significantly higher in the Iranian population according to angiographic classification, there was no significant difference in vascular involvement between the two countries (p=0.034, 0.012, 0.003 and 0.001, respectively). There was no statistically significant difference between the patterns of vascular involvement in the Iranian and Turkish populations, de-

spite the fact that both populations exhibited distinct patterns of distribution.
Moreover, there were 12 increased wall thickness, 19 stenoses, 4 occlusions, 1 aneurysm, and 1 dilation in the Iranian population and 0 increased wall thickness, 6 stenoses, 1 aneurysm, and 0 dilation in the Turkish population in the right subclavian artery (p=0.014).
Also included in this study were 10 Iranian patients (13.2%) and 12 Turkish patients (27.3%) who underwent stenting for stenosis or occlusion in renal and subclavian arteries, respectively (p=0.048).

Echocardiographic findings

In this study, 59 Iranian patients and 23 Turkish patients underwent TTE evaluation, with the majority exhibiting normal LV function with an EF greater than 50% (86.4% in Iranian and 95.7% in Turkish). Aside from this, 8 Iranian patients (13.6%) and one Turkish patient (4.3%) had reduced LVEF and systolic dysfunction at the time of disease diagnosis. None of these patients had previously been diagnosed with cardiac disorders. In Iranian and Turkish cases, the mean ePAP was 27.7±8 and 29.0±17.0 mmHg, respectively (p=0.4).
Only 4 Iranian patients and 3 Turkish patients had a PAP greater than 40 mmHg. Additionally, 10 Iranian patients (12.2) had diastolic dysfunction (DD) at the time of disease diagnosis, with all but one having grade 1 DD. In addition, the most prevalent type of valve involvement was aortic insufficiency, which affected 31.7% of the Iranian population and 47.7% of the Turkish population (p=0.36). Moreover, tricuspid insufficiency (TI) was significantly higher in the Turkish population (38.6%) compared to the Iranian population (23.2%) (p=0.04). Mitral regurgitation (MR) occurred in 43.9% of Iranian patients and in 50% of Turkish patients (p=0.6).

Treatment regimens

At the time of the study, both Iranian and Turkish patients relied primarily on glucocorticoids (89.0% *vs* 100%), followed by methotrexate (MTX) (62.1% *vs* 86.3%) and azathioprine (AZA) (36.5% *vs* 38.6%). In addition, aspirin, anti-hypertensive medications, and statins were utilized by 57.3%, 48.7%, and 35.3% of Iranian patients and 86.3%, 56.8%, and 9.0% of Turkish patients, respectively. In both countries, there was no significant difference between the types of drug regimens.

DISCUSSION

In this study, we compared the overall clinical picture of Iranian and Turkish TA patients, with a particular emphasis on their clinical manifestation and pattern of vascular involvement. According to our knowledge, this is the largest series of TA patients evaluated in Iran in terms of their clinicodemographic characteristics and vascular imaging findings, and it is also the largest registry of TA in Bursa, Turkey. In addition, this is the first study to compare the two countries.
In our patient cohort, the average age of disease onset in Iranian patients was 29.2±11.6 years, which was comparable to studies from the United States, India, and France, where it ranged from 29.2 to 30.2 years (18-20). However, the average age at onset of disease for Turkish patients was 32.8±11 years. Japanese (35 years, quartiles 1-3, 22-56.8 years) and Chinese (34.2 years±14) cohorts reported a later onset age (21, 22). This difference, although not significant, may be attributable to the influence of genetics and ethnicity on the disease's clinical presentation (5). Nonetheless, the older age at onset in some regions may be attributable to the rarity of TA and its non-specific early symptoms, which may delay its diagnosis. It is possible that in regions with an earlier age at onset, TA is accompanied by more severe and distinct symptoms that prompt the diagnosis (23).
Similar to previous studies from Norway (9:1) (6), Turkey (8.2:1) (24), and Korea (7.9:1), the female-to-male ratio in our study was approximately 8.7:1 (25). Reports from the United States (4.2:1), Japan (5:1), and South Africa (5.8:1) showed a lower ratio (6, 18, 21, 24, 26, 27). The female predominance pattern of TA under-

scores the significance of gender in the pathophysiology of TA. However, the lower prevalence of TA in men could be the result of physicians' lack of awareness of this rare disease in male patients. Alternatively, male patients may be more reluctant to seek medical care for non-specific symptoms that could be the earliest indications of TA. Significant delay between disease onset and diagnosis, as reported by the majority of studies, is in keeping with this hypothesis (6, 24, 28). Finally, male patients could suddenly die because of a catastrophic condition, such as a ruptured aneurysm or massive MI, without the underlying cause being identified (6, 21, 29, 30). In our study, male patients exhibited more severe symptoms, such as CVA, MI, and seizure. Based on this finding and the hypothesis that male patients may be underdiagnosed, males may have a more diffuse form of TA, whereas females' TA is more likely to involve the aortic arch and its branches (31).

The prevalence of TA clinical manifestations ranges from systemic manifestations to vascular signs and symptoms (6, 18, 20, 24, 28, 32). It differed between the two populations of our study: upper limb claudication was more prevalent in the Turkish population with a higher frequency of right subclavian involvement with occlusive lesions. Other studies in Turkey confirm that claudication of the upper limb and involvement of Type I vessels were common clinical manifestations in this population (24, 33). As these manifestations are partly based on patient reports, variations may be due to a different susceptibility to these subjective symptoms (34).

The majority of our patients in both countries showed absent pulses, asymmetrical blood pressure, and bruits. Limb claudication and fatigue were the most prevalent subjective symptoms overall, with nearly half of the patients reporting them. Based on our findings, the subclavian artery was the most frequently involved artery in TA. Left radial artery pulses were typically weak or absent, and the carotid artery was the vessel in which bruits were most frequently auscultated. These findings are similar to those of other cohorts from China (28), Korea (27), Japan (21), Iran (35), the United States (18), Turkey (24) and France (20). Moreover, because these signs are more pronounced in easy-to-access body areas, such as the wrists and neck, they can be detected through a quick and straightforward physical examination.

The most prevalent angiographic classification types in Iran, according to our study, were types V and I, with a prevalence of 41.0% each, followed by types IIb (8.2%), IIa (5.4%), and IV (4.1%). Similar to our findings, type V was the most frequently reported classification worldwide, with prevalence ranging from 25.8% in Japan (21) to 69.0% in Mexico (32). It appears that type V and I comprised the majority of cases in the majority of studies. For example, the prevalence of type V and I was 69% and 19% in Mexico (32), 60.8% and 22.1% in China (28), 50.8% and 32.1% in Turkey (24), 47.6% and 24.4% in France (20), and 47.6% and 24.4% in Japan (21). In our study of the Turkish population, type I was the most prevalent (47.7%), followed by type V (38.6%), type IIb (8.2%), type III (2.2%), type IV (2.2%), and type IIa (2.2%) (0%). These findings were consistent with a Norway study which found that type I was more prevalent among North European patients (48%), while type V was more prevalent among Asian/African immigrants (46.7%) (6).

In contrast to the majority of other studies, we found no type III or IIa vascular involvement in Iranian or Turkish patients. This may be related to the specific symptoms exhibited by these patients. As a result of the involvement of the descending aorta in this type, the majority of patients exhibit vascular abdominal pain or uncontrolled hypertension. The absence of type III and IIa in our study may be due to a referral bias, as the majority of these patients are not diagnosed with TA and are not referred to a rheumatology service. The progression of the disease to a more severe form, may also be a contributing factor.

Subclavian vessels were the most frequently affected among our patients, followed by the common carotid, abdominal aorta, and

vertebral artery. A high proportion of these involvements were consistent with the most common and fatal clinical manifestations. These included upper limb claudication, cerebrovascular accident, recurrent syncope, myocardial infarction, and uncontrolled hypertension. This finding should serve as a reminder to physicians to be on the lookout for peripheral pulses, vascular murmur, and blood pressure in both arms in young patients, as well as to check for other possible and straightforward symptoms.

According to our findings, the superior mesenteric, pulmonary, and coronary arteries were more frequently affected in Iranian patients. Only patients with clinical manifestations, such as abdominal angina and cardiopulmonary symptoms, underwent these imaging procedures. In contrast, a previous genome-wide association study of other rheumatic disorders revealed a high degree of similarity between the Iranian and Turkish populations (36).

Stenting procedures in renal and subclavian arteries were significantly more frequent in the Turkish population, which may be attributable to the prevalence of hypertension and of subclavian occlusive lesions in Turkish patients. According to previous studies, the Chinese population had 8.5% of renal and subclavian arteries with prominent stenting, similar to the Iranian population (28). In contrast, studies conducted in the United States (18) and France (20) revealed rates of angioplasty with or without stenting due to claudication, hypertension, or ischemia that were more comparable to the Turkish population. This difference appears to be due ethnicity, severity of disease, and number of occlusive lesions, as well as uncontrolled hypertension, which results in earlier intervention. This reminds us that we should keep close follow-up by imaging protocols for TA patients in order to diagnose the need for intervention early and prevent further complications.

Finally, a number of significant limitations must be considered. First, this study was affected by referral bias because patients were recruited from university centers. Population-based national studies are also needed. Second, the number of cases is small.

In conclusion, our findings suggest that Iranian and Turkish patients share similar clinicodemographic characteristics and patterns of vascular involvement. Despite the fact that Iranian patients were younger at the onset of disease, it appears that both countries had a significant female preponderance. Claudication of the upper limb was more prevalent in the Turkish population due to a more occlusive lesion in the right subclavian artery. This study also revealed that type I and type V were the most prevalent vessel types in Iran and Turkey, respectively.

Compliance with ethical standards

The cross-sectional proposal of this study was approved by the Ethics Committee of School of Medicine, Tehran University of Medical Sciences with the following approval ID: IR.TUMS.MEDICINE.REC.1397.849.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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