Features of the Onset of Takayasu's Arteritis According to Gender

Andrea Rocha de Saboia Mont'Alverne, Luiz Eduardo de Paula, Samuel Katsuyuki Shinjo

Divisão de Reumatologia - Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo – Brazil

Abstract

Background: Although there are various published epidemiological studies regarding Takayasu's arteritis (TA), none have analyzed the influence of gender on the clinical and laboratory manifestations or vascular alterations at disease onset.

Objectives: To analyze the influence of gender on clinical and laboratory manifestations and variations in vascular imaging at TA onset.

Methods: A retrospective, unicentric cohort study that evaluated 55 consecutive TA patients between 1982 and 2012. All available clinical data and laboratory test results related to the onset of the disease were analyzed. We included only patients aged 12-35 years at diagnosis to exclude age-related factors.

Results: We analyzed 17 men and 38 women, mostly Caucasian, with a comparable mean age between genders. There was no gender difference regarding the clinical or laboratory characteristics, comorbidities, or smoking habit, except for abdominal pain, which was more common in men. Regarding vascular lesions, the presence of ascending aortic aneurysms was significantly more frequent in males. Male gender represented an independent risk factor for the occurrence of abdominal pain and ascending aortic aneurysms in TA patients.

Conclusion: Abdominal pain and ascending aortic aneurysms occurred more frequently in men with TA, suggesting a more severe disease profile in males. (Arq Bras Cardiol. 2013;101(4):359-363)

Keywords: Takayasu Arteritis / epidemiology; Male; Female; Cohort Studies; Aortic Aneurysm, Abdominal; Abdominal Pain.

Introduction

Takayasu's arteritis (TA) is a type of primary systemic vasculitis that affects medium and large arteries, including the aorta and its main branches, as well as the pulmonary and coronary arteries[1]. The pathophysiology of TA is characterized by vessel wall inflammation, leading to thickening, stenosis, dilatation, and/or aneurysm formation of the affected vessels[2]. The signs and symptoms that reflect the context of the systemic inflammation or ischemia of an organ or limb include the presence of claudication, angiodynia, peripheral pulselessness, murmurs, severe systemic arterial hypertension, myocardium infarction, and ischemic stroke, among others[2,3].

In general, systemic autoimmune diseases affect more women than men, by a ratio of 2–10:1. Systemic lupus erythematosus and Sjogren's syndrome, for example, have ratios of 7–10:1, whereas rheumatoid arthritis and systemic sclerosis have ratios of 2–3:1[4], while TA also tends to affect women more often, with a ratio of 1.2–29:1[3,5].

Mailing Address: Samuel Katsuyuki Shinjo •
Division of Rheumatology, Faculdade de Medicina da Universidade de São Paulo - Av. Dr. Arnaldo, 455, 3º andar, sala 3150. Postal Code 01246-903, São Paulo, Brazil
E-mail: samuel.shinjo@gmail.com
Manuscript received December 10, 2012; revised December 22, 2012; accepted March 28, 2013.

DOI: 10.5935/abc.20130180

Although there have been various epidemiological studies regarding TA, none have reported the influence of gender on the clinical and laboratory manifestations and the vascular alterations at the onset of the TA. Although Sharma and Jain[6] studied a possible role of sex in the distribution of the vascular lesions in TA and found a tendency for greater involvement of the abdominal aorta in men and the aortic arch and its branches in women, they did not specify whether their findings were cumulative or related to disease onset.

Thus, in the present study, we evaluated the initial clinical manifestations and the vascular alterations at the onset of TA according to gender.

Methods

We evaluated 55 consecutive TA patients (17 men and 38 women) treated at the vasculitis unit of our tertiary facility between 1982 and 2012. We included only patients who were aged between 12 and 35 years at TA diagnosis and who met at least three of the six American College of Rheumatology classification criteria (1990)[7]. The study protocol was approved by our local ethics committee.

Demographic data, clinical manifestations, and vascular images were obtained through a systematic review of the patients' medical records. The follow parameters were analyzed: (A) clinical manifestations: constitutional symptoms (weight loss, fever, fatigue), headache, dizziness, visual

impairment (blindness), seizures, carotidynia, claudication, abdominal pain, chest pain, dyspnea, articular manifestations (arthritis/arthralgia), and erythema nodosum; (B) laboratory findings: C-reactive protein (CRP) (reference value: < 5 mg/L) and erythrocyte sedimentation rate (ESR) (reference value: < 19 mm/1st hour); (C) comorbidities: myocardium infarction, ischemic stroke, systemic arterial hypertension, heart failure, type 2 diabetes mellitus, and dyslipidemia; (D) habit: smoking; and (E) echocardiography: aortic insufficiency.

All vascular images were obtained via angiography or computed tomography angiography, in which we evaluated the following parameters: stenosis/occlusion, aneurysm/vascular ectasia, and the anatomical location of these lesions.

The results were expressed as the means ± standard deviation (SD) or as percentages. We used the Student's *t*-test to analyze the parametric data and the Mann-Whitney U-test for the nonparametric data. The 95% confidence intervals (95% CI) of the percentages were calculated by binomial distribution. All calculations were performed using STATA ver. 7.0 statistical software (Stata Corp., College Station, TX, USA). A p-value < 0.05 was considered statistically significant.

Results

We analyzed records of 17 men and 38 women with TA, who were mostly Caucasian and had a comparable mean age between genders (Table 1). The clinical and

Table 1 - Demographic, clinical, and laboratory characteristics of Takayasu's arteritis according to gender

Features	Male (n = 17)	Female (n = 38)	p
Age at disease onset ± SD (years)	23.5 ± 7.6	25.3 ± 5.5	0.371
Ethnicity: white (%)	9 (52.9)	28 (73.7)	0.130
Clinical onset manifestations			
Weight loss (%)	8 (47.1)	9 (23.7)	0.083
Fever (%)	7 (41.2)	10 (26.3)	0.270
Fatigue (%)	2 (11.8)	6 (15.8)	0.696
Headache (%)	1 (5.9)	6 (15.8)	0.308
Dizziness (%)	0	2 (5.3)	0.335
Visual disturbances (%)	1 (5.9)	2 (5.3)	0.926
Amaurosis (%)	1 (5.9)	0	0.131
Convulsions (%)	1 (5.9)	0	0.131
Carotidynia (%)	3 (17.6)	8 (21.1)	0.770
Upper limb claudication (%)	5 (29.4)	16 (42.1)	0.371
Lower limb claudication (%)	2 (11.8)	12 (31.6)	0.119
Abdominal pain (%)	6 (35.3)	2 (5.3)	0.004
Chest pain (%)	0	6 (15.8)	0.083
Dyspnea (%)	1 (5.9)	6 (15.8)	0.308
Articular manifestations (%)	1 (5.9)	4 (10.5)	0.165
Erythema (%)	1 (5.9)	4 (10.5)	0.580
Elevated ESR and/or CRP (%)	6 (35.3)	23 (60.5)	0.613
Aortic insufficiency (%)	3 (17.6)	6 (15.8)	0.863
Comorbidities			
Ischemic stroke (%)	1 (5.9)	10 (26.3)	0.143
Systemic arterial hypertension (%)	10 (58.8)	20 (52.6)	0.370
Cardiac insufficiency (%)	0	1 (2.6)	0.500
Myocardium infarction (%)	0	1 (2.6)	0.500
Diabetes mellitus (%)	0	2 (5.3)	0.335
Dyslipidemia (%)	2 (11.8)	12 (31.6)	0.119
Smokers (%)	2 (11.8)	4 (10.5)	0.892

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SD: standard deviation.

laboratory characteristics and comorbidities of patients at disease onset are shown in Table 1. There was no gender difference regarding the distribution of signs and symptoms, except for abdominal pain (35.3% vs. 5.3%, p = 0.004, in men and women, respectively). The presence of aortic insufficiency, elevation of ESR and CRP, comorbidities, and habit (smoking) were also similar between genders.

Regarding vascular lesions found in the first imaging for each patient, we observed that there was no gender difference in the frequency or the location of the stenoses/occlusions, which were more common in the carotid and subclavian arteries in women than men (Table 2). However, the presence of ascending aortic aneurysms was significantly more frequent in men (35.3 vs. 10.5%, p = 0.028), although other aneurysm locations did not differ between genders.

Multivariate analysis showed that male gender was a risk factor for the occurrence of abdominal pain (OR, 18.75; 95% CI, 2.89–121.54) and aortic aneurysm (OR, 9.51; 95% CI, 1.94–46.70) (Table 3).

Discussion

To our knowledge, the present study is the first to analyze the presentation of TA in terms of clinical manifestations and vascular imaging alterations according to gender. Compared to women, men had a higher prevalence of abdominal pain and ascending aortic aneurysm at diagnosis of TA.

Despite the existence of various epidemiological series regarding TA patients [3,8-19], none have compared disease presentation between men and women. In this study, all of the parameters refer clearly to the onset of symptoms before any drug or surgical treatment is initiated. Furthermore, we evaluated only patients aged between 12 and 35 years to exclude clinical manifestations, comorbidities, or vascular changes that could be related to advanced age rather than to TA alone.

Gender is likely a determinant in the prognosis of several rheumatic diseases. For example, systemic lupus erythematosus tends to have a worse prognosis

Table 2 - Angiographic characteristics of Takayasu's arteritis according to gender

Vessels	Stenosis / Occlusion			Aneurysm /Ectasia		
	Male	Female	p	Male	Female	p
Left coronary (%)	0	1 (2.6)	1.000	0	0	1.000
Right coronary (%)	0	1 (2.6)	1.000	0	0	1.000
Left vertebral (%)	0	6 (15.8)	0.131	1 (5.9)	0	0.131
Right vertebral (%)	0	6 (15.8)	0.131	1 (5.9)	0	0.131
Left carotid (%)	7 (41.2)	20 (52.6)	0.487	0	0	1.000
Right carotid (%)	6 (35.3)	20 (52.6)	0.200	0	0	1.000
Left subclavian (%)	6 (35.3)	21 (55.3)	0.926	1 (5.9)	2 (5.3)	0.926
Right subclavian (%)	4 (23.5)	14 (36.8)	0.552	1 (5.9)	1 (2.6)	0.552
Brachiocephalic trunk (%)	1 (5.9)	5 (13.2)	0.391	2 (11.8)	2 (5.3)	0.391
Pulmonary trunk (%)	0	1 (2.6)	0.500	0	1 (2.6)	0.500
Aortic						
Ascendant (%)	1 (5.9)	2 (5.3)	0.926	6 (35.3)	4 (10.5)	0.028
Cross (%)	1 (5.9)	4 (10.5)	0.168	2 (11.8)	1 (2.6)	0.168
Thoracic (%)	1 (5.9)	7 (18.4)	0.108	4 (23.5)	3 (7.9)	0.108
Abdominal (%)	2 (11.8)	7 (18.4)	0.552	1 (5.9)	1 (2.6)	0.552
Infrarenal (%)	2 (11.8)	8 (21.1)	0.131	1 (5.9)	0	0.131
Left renal (%)	7 (41.2)	5 (13.2)	0.500	0	0	0.500
Right renal (%)	6 (35.3)	5 (13.2)	0.131	1 (5.9)	1 (2.6)	0.131
Upper mesenteric (%)	3 (17.6)	7 (18.4)	0.945	0	0	1.000
Lower mesenteric (%)	2 (11.8)	3 (7.9)	0.645	0	0	1.000
Celiac trunk (%)	2 (11.8)	4 (10.5)	0.131	1 (5.9)	0	0.131
Left iliac (%)	1 (5.9)	6 (15.8)	0.308	0	0	1.000
Right iliac (%)	1 (5.9)	5 (13.2)	0.424	0	0	0.500

Table 3 - Multivariate analysis for gender

Variate	OR	95% CI
Age at disease onset	0.96	0.86–1.07
Abdominal pain	18.75	2.89–121.54
Ascendant aortic aneurysm	9.51	1.94–46.70

in men, although this view remains controversial[20-23]. In rheumatoid arthritis, female gender has been associated with higher scores of disease activity[24] and is an established predictor of radiographic progression[25]. Furthermore, the inflammatory response appears to be more severe in women than in men as well as the presence of giant cell arteritis and polymyalgia rheumatica[26]. However, there are no studies that have evaluated sex as a determining factor in TA prognosis. Our results showed a strong association between the presence of aortic aneurysm and male gender, thereby correlating this gender to a poor prognostic factor.

Other factors classically associated with poor prognosis in TA include the following: retinopathy, hypertension, severe aortic regurgitation, and the presence of aortic or arterial aneurysm, as mentioned previously[27]. Subsequently, the presence of severe functional disability and cardiac involvement were reported as predictors of either death or major events on follow-up[28]. Sharma and Jain[6] reported a trend toward a higher frequency of hypertension in men with TA compared with women, but this was not observed in the present study. Chugh et al[29] studied renovascular hypertension in Indians with AT and also found no difference between genders. Aortic regurgitation was also similar in both sexes in our series, in contrast to the findings of Kobayashi and Numano[30], who reported a higher prevalence of aortic regurgitation in women.

Our study was limited by its retrospective nature and complicated by typical problems of this type of cohort. Furthermore, the collected data were dependent on the medical records and even though all of the variables were true at the time of diagnosis, we do not know if they accurately reflected manifestations at disease onset.

Conclusion

Abdominal pain and ascending aortic aneurysms occurred more frequently in men with TA and the male gender was an independent risk factor for such findings. Nonetheless, further studies will be needed to confirm male gender as a predictor of poor prognosis in TA.

Author contributions

Conception and design of the research and Statistical analysis: Shinjo SK; Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: MontAlverne ARS, Paula LE, Shinjo SK.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

References

1. Kerr GS. Takayasu's arteritis. Rheum Dis Clin North Am. 1995;21(4):1041-58.
2. Johnston SL, Lock RJ, Gompels MM. Takayasu arteritis: a review. J Clin Pathol. 2002;55(7):481-6.
3. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, et al. Takayasu arteritis. Ann Intern Med. 1994;120(11):919-29.
4. Lockshin MD. Sex differences in autoimmune disease. Lupus. 2006;15(11):753-6.
5. Deutsch V, Wexler L, Deutsch H. Takayasu's arteritis: an angiographic study with remarks on ethnic distribution in Israel. Am J Roentgenol Radium Ther Nucl Med. 1974;122(1):13-28.
6. Sharma BK, Jain S. A possible role of sex in determining distribution of lesions in Takayasu arteritis. Int J Cardiol. 1998;66 Suppl 1:S81-4.
7. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum. 1990;33(8):1129-34.
8. Zheng, Fan D, Liu L. Takayasu arteritis in China: a report of 530 cases. Heart Vessels Suppl. 1992;7:32-6.
9. Piyachon C, Suwanwela N. Takayasu arteritis in Thailand. Heart Vessels Suppl. 1992;7:60-7.
10. Koide K. Takayasu arteritis in Japan. Heart Vessels Suppl. 1992;7:48-54.
11. Ureten K, Ozturk MA, Onat AM, Ozturk MH, Ozbalkan Z, Guvener M, et al. Takayasu's arteritis: results of a university hospital of 45 patients in Turkey. Int J Cardiol. 2004;96(2):259-64.
12. Park MC, Lee SW, Park YB, Chung NS, Lee SK. Clinical characteristics and outcomes of Takayasu's arteritis: analysis of 108 patients using standardized

criteria for diagnosis, activity assessment, and angiographic classification. Scand J Rheumatol. 2005;34(4):284-92.

13. Vanoli M, Daina E, Salvarani C, Sabbadini MG, Rossi C, Bacchiani G, et al. Takayasu's arteritis: a study of 104 Italian patients. Arthritis Rheum. 2005;53(1):100-7.

14. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. Arthritis Rheum. 2007;56(3):1000-9.

15. Soto ME, Espinola N, Flores-Suarez LF, Reyes PA. Takayasu arteritis: clinical features in 110 Mexican Mestizo patients and cardiovascular impact on survival and prognosis. Clin Exp Rheumatol. 2008;26(3 Suppl 49):S9-15.

16. Watts R, Al-Taiar A, Mooney J, Scott D, Macgregor A. The epidemiology of Takayasu arteritis in the UK. Rheumatology (Oxford). 2009;48(8):1008-11.

17. Karageorgaki ZT, Bertsias GK, Mavragani CP, Kritikos HD, Spyropoulou-Vlachou M, Drosos AA, et al. Takayasu arteritis: epidemiological, clinical, and immunogenetic features in Greece. Clin Exp Rheumatol. 2009;27(1):S33-9.

18. Arnaud L, Haroche J, Limal N, Toledano D, Gambotti L, Costedoat Chalumeau N, et al. Takayasu arteritis in France: a single-center retrospective study of 82 cases comparing white, North African, and black patients. Medicine (Baltimore). 2010;89(1):1-17.

19. Dreyer L, Faurschou M, Baslund B. A population-based study of Takayasu's arteritis in eastern Denmark. Clin Exp Rheumatol. 2011;29(1 Suppl 64):S40-2.

20. Specker C, Becker A, Lakomek HJ, Bach D, Grabensee B. Systemic lupus erythematosus in men - a different prognosis? J Rheumatol. 1994;53(6):339-45.

21. Miller MH, Urowitz MB, Gladman DD, Killinger DW. Systemic lupus erythematosus in males. Medicine (Baltimore). 1983;62(5):327-34.

22. Molina JF, Drenkard C, Molina J, Cardiel MH, Uribe O, Anaya JM, et al. Systemic lupus erythematosus in males: a study of 107 Latin American patients. Medicine (Baltimore). 1996;75(3):124-30.

23. Garcia MA, Marcos JC, Marcos AI, Pons-Estel BA, Wojdyla D, Arturi A, et al. Male systemic lupus erythematosus in a Latin American inception cohort of 1214 patients. Lupus. 2005;14(12):938-46.

24. Iikuni N, Sato E, Hoshi M, Inoue E, Taniguchi A, Hara M, et al. The influence of sex on patients with rheumatoid arthritis in a large observational cohort. J Rheumatol. 2009;36(3):508-11.

25. Syversen SW, Gaarder PI, Goll GL, Ødegård S, Haavardsholm EA, Mowinckel P, et al. High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: results from a 10-year longitudinal study. Ann Rheum Dis. 2008;67(2):212-7.

26. Narvaez J, Nolla-Solé JM, Valverde-García J, Roig-Escofet D. Sex differences in temporal arteritis and polymyalgia rheumatica. J Rheumatol. 2002;29(2):321-5.

27. Ishikawa K, Maetani S. Long-term outcome for 120 Japanese patients with Takayasu's disease: clinical and statistical analyses of related prognostic factors. Circulation. 1994;90(4):1855-60.

28. Subramanyan R, Joy J, Balakrishnan KG. Natural history of aortoarteritis (Takayasu's disease). Circulation. 1989;80(3):429-37.

29. Chugh KS, Jain S, Sakhuja V, Malik N, Gupta A, Sehgal S, et al. Renovascular hypertension due to Takayasu's arteritis among Indian patients. Q J Med. 1992;85(307-308):833-43.

30. Kobayashi Y, Numano F. 3. Takayasu arteritis. Intern Med. 2002;41(1):44-6.