Disease Characteristics of Takayasu's Arteritis Among Filipino Patients Seen at Rheumatology Clinics

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Abstract

Introduction: Takayasu's arteritis (TA), a large vessel vasculitis has various initial presenting manifestations; making it difficult to diagnose. Hence, the number of those with the disease in the population is underestimated. The study intends to update local data and to describe different presentations of the disease to enhance awareness for TA.

Methods: This is a retrospective study done in a tertiary government hospital. Twenty-two out of twenty three charts of patients diagnosed with TA based on the 1990 ACR criteria were reviewed. Demographic profile, initial clinical manifestations, imaging, treatment and outcomes were collected. Descriptive statistics was applied. Institutional Review Board approval was obtained prior to study initiation.

Results: Majority (90.1%) were female; mean age at onset of symptoms and at diagnosis were 30.4 (+12.3)years and 33.2 (+12.0)years respectively. The common reasons for consult were hypertension (26.3%), claudication (21.1%) and abdominal pain (11%). Laboratories showed elevated erythrocyte sedimentation rate (87.5%), leukocytosis (43.8%), anemia (31%) and thrombocytosis (4.5%). Common imaging findings were cardiomegaly (27.3%), aortic regurgitation (27.3%) and carotid stenosis (18.2%). CT angiogram in 90% of cases demonstrated arterial wall narrowing. Other findings were aneurysm (31.8%), contour irregularities (13.6%) and femoral artery occlusion (4.5%). Treatment for active disease were glucocorticoids alone (44%) and combined glucocorticoids and other immunosuppressants (56%). Of the 22 records reviewed, six patients (27%) had stroke. Four (18.2 %) had different surgical procedures; ray amputation of toe for digital ischemia, embolectomy for digital gangrene, balloon angioplasty of the renal artery and renal angioplasty for stenosis. Two (9.1%) who had pregnancies after TA diagnosis had premature deliveries without neonatal complications. No mortality was recorded over the mean follow-up of 49.33 patient-years.

Conclusion: Clinicians should be aware of the different initial presenting signs and symptoms of TA since development of collateral circulation may mask other symptoms. Thus, thorough history and physical assessment are essential tools in the diagnosis of TA.

Keywords: takayasu's arteritis, rheumatology clinics

Introduction

Takayasu's arteritis (TA) is a chronic inflammatory disease that primarily involves large vessels such as aorta and its main branches, including pulmonary and coronary arteries.[1] The true incidence and prevalence of TA is underestimated since it can mimic other diseases.[2] In the United States, the incidence of TA is estimated to be 2.6/million people, 1.26/million in Northern Europe and 1/3000 autopsies in Japan. In our country, there is still a gap in the knowledge regarding the exact incidence and prevalence of Takayasu's arteritis.[3] Previous data from different countries reported varied presentation and prognosis of TA. It can affect both genders at any age and in all ethnic groups. In Asia and Middle East, it is more common in young females than in Europe and North America, although precise data of its prevalence and characteristics are not available.[1,4] The initial manifestations of Takayasu's Arteritis are not clear cut and sometimes confusing hence diagnosis is often delayed.

The researchers aim to describe the disease characteristics of Filipino patients with Takayasu's arteritis in terms of their initial clinical presentation, initial laboratory parameters and imaging modalities; treatment and outcome based on latest follow up.

Methods

This is a retrospective study wherein adults aged 19 years old above, diagnosed with Takayasu's arteritis based on the 1990 ACR criteria and seen in a tertiary government hospital (both in-patient and outpatient) were included. Non-probability sampling was used.

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Patients included in the study were those seen by the physicians of the Section of Rheumatology from 1991 to 2015. The charts of patients that were either admitted or had out-patient department (OPD) consult were retrieved. Out of the 23, only one chart was not included since it could not be located during the study. All charts included were adjudicated by at least two investigators independently to ascertain the diagnosis of TA. A third investigator was present to settle potential conflicts. Data on demographic profile, initial presenting clinical manifestations, laboratories such as haemoglobin, ESR, white blood cell, platelet count, creatinine and imaging studies (chest x-ray, 2D echocardiography, carotid duplex, whole abdominal ultrasound, computed tomography with angiogram) done were collected. Treatment and outcomes or complications were also included in the data collection. Demographic and clinical characteristics were expressed as frequencies and percentage.

This study has been approved by the University of the Philippines Manila Research Ethics Board (UPMREB) PGH Panel. The patients' charts were given a corresponding code number to secure their identities. This was purely chart review with no patient interaction. There was no monetary compensation. The information gathered anonymized and confidential.

Results

Twenty-two out of the 23 charts of patients with TA from 1991 to 2015 were included in the study. There was female preponderance with 20 patients (90%). The mean age at onset of symptoms is 30.4 years (+12.3) and the mean age at the time of diagnosis is 33.2 years (+12.0). Two (9.1%) of the patients had a history of smoking.

The most common complaints and/or reasons for referral were presented in Table I. Some of the patients reported history of other symptoms that were not present during the index consultation. These included weight loss, easy fatigability, headache, blurring of vision, dizziness and dyspnea. The most common signs were pulse abnormality (86.4%), abnormalities in the blood pressure, of which 77.8% had asymmetric blood pressure and 22.2% had absent blood pressure, bruit (50%) and murmur (22.7%).

In our study, 87.5% of patients had increased ESR. Other findings included anemia (31%) and leukocytosis (43.8%). Only one (6.7%)of our patients had elevated platelet count. (Table II)

Initial imaging studies usually requested short of CTA included chest x-ray, 2D echocardiography, carotid duplex and whole abdominal ultrasound. On chest radiographs, six (27.3%) patients had cardiomegaly and six patients had aortic regurgitation and concentric left ventricular hypertrophy on 2d echocardiography. One patient was noted to have narrowing of descending aorta. Four patients (18.2%) who underwent carotid duplex had carotid stenosis. On whole abdominal ultrasound, two patients had dilated abdominal aorta.

CT angiogram showed abnormalities in different arteries. (Table III) The most common finding is stenosis followed by aneurysmal formation.

For the treatment, eight (36%) patients received steroids alone while 54% received steroid with steroid-sparing agents (such as azathioprine in 18.2% and methotrexate in 36.4%).

Table I. Clinical features of patients with TA (n=22)

	Duration of signs and symptoms prior to diagnosis (months)	Index symptoms at consult n (%)	Ever present n (%)
Hypertension	116.5	17 (77.3)	17 (77.3)
Claudication	10.9	13 (59.1)	13 (59.1)
Weight loss	5.5	5 (22.3)	6 (27.3)
Easy fatigability	7	3 (13.6)	6 (27.3)
Visual abnormality*	44.3	3 (13.6)	5 (22.3)
Headache	131	1 (4.5)	4 (18.2)
Dizziness	11.5	4 (18.2)	4 (18.2)
Raynaud's	1.75	4 (18.2)	4 (18.2)
Arthralgia	23.3	2 (9.1)	4 (18.2)
Dyspnea	104	3 (13.6)	3 (13.6)
Chest pain	6	2 (9.1)	2 (9.1)
Fever	7.7	2 (9.1)	2 (9.1)
Abdominal pain	2.5	2 (9.1)	2 (9.1)
Blood pressure abnormality Asymmetric BP Absent BP	12	18 (81.8) 14 (77.8) 4 (22.2)	18 (81.8)
Pulse abnormality Asymmetric Absent	0	19 (86.4) 11 (57.9) 8 (42.1)	19 (86.4)
Bruit Carotid Subclavian Abdominal	0	11 (50) 8 (72.7) 1 (9.1) 4 (36.4)	11 (50)
Murmur	0	5 (22.7)	5 (22.7)

**blurring of vision*

Table II. Laboratory findings at index consult of adult patients with TA

	Mean	SIGNIFICANT FINDINGS	n (%)
ESR (mm/hr) (n=16/SD)	44.6±22.4	Elevated ESR	14 (87.5)
Hemoglobin (g/dL) (n=16)	124.9	Anemia	5 (31.1)
White blood cells (/mm3) (n=16)	10,900.0	Leukocytosis	7 (43.8)
Platelet count (/mm^3) (n=15)	330,400.0	Thrombocytosis	1 (6.7)
Creatinine (umol/L) (n=14)	74.7	Elevated creatinine	2 (14.3)

Those who had cerebrovascular disease (stroke) were given aspirin (4%) and warfarin (3%).

Complications of TA included stroke, seizures, myocardial infarction and surgeries for symptoms of insufficiency. In our patients, 10 patients had apparent good response to medical treatment without onset of complications. Six (27%) had stroke. Four (18.2 %) underwent different surgical procedures for which one had ray amputation of left big toe for digital ischemia while one patient had embolectomy secondary to digital gangrene. Two patients who had renal artery stenosis had renal angioplasty and balloon angioplasty of the renal artery respectively. Two patients who were pregnant during the course of the disease had premature deliveries but the infants were noted to be appropriate for age.

Ophthalmologic findings include two hypertensive retinopathies (one had multiple lacunar infarcts and one had associated vasculitic retinopathy). Only one patient had chronic renal disease on latest follow up. One patient had adjustment disorder (depressed mood and panic attacks) and is currently under the care of psychiatrist. No mortality was recorded based on a mean of follow up of 49.33 patient-years.

Table III. CT angiogram findings in patients with TA

	Narrowing/ stenosis (90%)	Aneurysm (31.8%)	Contour irregularities (13.6%)	Occlusion (4.5%)
Descending aorta	1	4	1	0
Abdominal aorta	1	3	0	0
Subclavian artery	6	0	1	0
Carotid artery	2	0	1	0
Celiac artery	2	0	0	0
Superior mesenteric artery	4	0	0	0
Inferior mesenteric artery	1	0	0	0
Renal artery	7	3	0	0
Iliac artery	1	0	0	0
Femoral artery	0	0	0	1

Discussion

In Takayasu's arteritis, reports on female to male ratio are diverse. In this study, majority are females (9:1). This is similar to other Asian countries (Japan and Korea), where in Korea the ratio is 6.6:1 as well as in Turkey (8.2:1).[1,5,6] In contrast to these studies, TA cases in India reported by Jain et al. in 2014 found no significant difference among sex while previous studies in India report male preponderance (1:6.4).[1,2]

Mean age of onset of symptoms and diagnosis in this study were 30.4 and 33.2 years respectively compared to other studies where the mean age of onset of symptoms was 30.2 years while mean age at diagnosis was 40.1 years.[1]The early detection or diagnosis in our study can be attributed to patients consulting early for symptoms and the high index of suspicion among clinicians prompting work-up and early referral to rheumatologists.

The clinical characteristics noted in our patients were comparable to the local studies done by Estrella AB et al. in 1999 and by Flauta et al in 1999.[7,8] In a study done in Korea, headache was the presenting symptom in 60% while in India, it was hypertension.[2,6] There is evident variety of symptoms at presentation. This may depend on the location of the involved artery and may be due to development of collateral circulation which could provide initial relief of the symptoms.[9]The diverse features of the disease are seen in different countries and are tabulated below. (Table IV)

Table IV. The most common signs and symptoms in our patients compared to previous studies done in the Philippines, India and Turkey

	Current	Flauta et al (1999) Phlippines N=67	Estrella AB et al (1999) Philippines (3 hospitals from 1968-1997) N=81	Jain SR et al (2009-2010) (2014) India N=30	Bicakcigil M et al (2009) Turkey N=248
Abnormalities in blood pressure (absent and asymmetric BP)	81.8%	36%	44%		81-88%
Pulses	86.4%				
Claudication	59.1%				48%
Hypertension	77.3%	63%	65%	83.3%	43%
Bruit	50%				77%
Weight loss	27.3%			13.3%	25%
Visual disturbance	22.3%	33%	31%	13.3%	21%
Headache	18.2%	45%	46%	83.3%	48%
Chest pain	9.1%	27%	30%		
Dyspnea				53.3%	22%
Syncope				20%	
Extremity pain					69%
Fatigue					56%

Almost 90% of our patients had elevated ESR which is consistent in other studies where it may be increased in as many as 80%. One-third of patients may have platelet counts that may exceed 500,000/mm^3. Creatinine is usually normal in patients with TA.[10]

Computed tomography with angiography (CTA) is the preferred imaging to identify pathologic vessels. This is not however always readily available in all institutions. Therefore, other imaging modalities are initially done to evaluate patients.[10] One of which is ultrasound. In TA, there is homogenous, diffuse wall thickening and what is seen in the sonography as the "macaroni sign". It is distinguished from arteriosclerosis where the wall thickening is inhomogenous. Stenosis or narrowing of aortoa in TA also involves long segments compared to short segments of atherosclerosis or fibromuscular dysplasia.[11] Other cardiac manifestations in 2D echocardiography with Doppler may be secondary to hypertension or complications of TA such as congestive heart failure. Aortic regurgitation (AR) is a significant finding as it often leads to dilatation of the left ventricle, mitral regurgitation and congestive heart failure.[10] Moriwaki et al. noted that many Japanese patients with TA had evidence of AR.[5]

The usual manifestation in CTA is mural thickening of the arteries. Calcification is also usually observed (27%) but it is difficult to distinguish from atherosclerosis.[9] In other studies, the most common artery abnormality noted in patients with TA were subclavian and common carotid artery stenoses followed by renal arteries. Often, the abdominal aorta is also involved.[5,6,9] With regard to angiographic classification of TA, 25% of patients in our study had type I, IV and V lesions. This is in contrast to reports in India where type III and type IV lesions were more prominent. On the other hand, types I and II are more frequently seen in Japan.[2,5,9]

There is no standard treatment for TA. Prior to giving pharmacological or surgical intervention, it is important to at least identify the phase of the disease. In the study by Bicakcigil, 93% of patients had active diseases hence were given steroids to control symptoms and induce remission. In India, only 15% were given glucocorticoids since most of the patients were already in their burnout phase.[1,2]

Immunossuppressives are also used as steroid-sparing agents to reach and maintain remission since prolonged use of steroids may lead to more serious complications. Among these, the most commonly used was methotrexate (63%). Others include cyclophosphamide, azathioprine, mycophenolate mofetil and leflunomide. Case reports and review of literature showed that anti-TNF and tocilizumab may be used in patients with refractory TA.[11,12] In our cohort, 36.4% were given steroids and methotrexate. Methotrexate was the most common steroid-sparing agent followed by azathioprine. None of the patients were given cyclophosphamide or anti-TNF agents.

Two pregnant patients in our cohort had premature deliveries but were born alive and suitable for age. Sharma et al., described 12 female patients with TA who had 24 pregnancies. Of the seventeen live babies born, five had intrauterine growth retardation and four had premature deliveries. This shows that normal spontaneous delivery with livebirths can be anticipated if TA is diagnosed early and hypertension is controlled.

Neurological and cardiac complications are critical in the evaluation and monitoring of patients with TA since these are important causes of mortality. In fact, according to Jain et al., patients with type I and Type II arteritis are more prone to develop stroke and aortic regurgitation.[2,9] This is comparable to our patients who had stroke (27.3%); four had type I lesions and two had type V lesions; but six (27.3%) of the patients who had aortic regurgitation did not have cerebrovascular disease.

Conclusion

Takayasu's arteritis is found in certain proportion of patients in the Philippines although it may not be reported as often. Establishing the diagnosis may be difficult due to its varied presentation. Therefore awareness of these manifestations is essential.

Laboratories included in the study were done at index consult with the rheumatology service hence the results may not represent the true initial findings during the first symptom of the disease. We recommend a database for these cases as well as for future ones to determine the true incidence and prevalence of TA in our country.

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APPENDIX A. Definition of Terms

a. Disease duration – duration of symptoms from the time of diagnosis to last consult
b. Index consult - initial consult with the rheumatologist
c. Elevated erythrocyte sedimentation rate (ESR) - more than 20 mm/hr
d. Anemia – hemoglobin of less than 12 g/dL in women and less than 13 g/dL in men
e. Leukocytosis – white blood cell count of more than 11,000/mm^3
f. Thrombocytosis – platelet count of more than 450,000/mm^3
g. Aneurysm - 50% increase in measurement of the usual diameter of an artery