Crimson Publishers
Wings to the Research

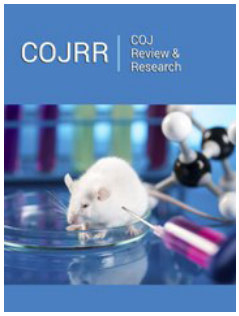
Mini Review

Takayasu's Arteritis: Etiopathogenesis and Treatment Strategies

Paul Gamboa*

Departamento de Intervenciones por Cateterismo, Argentina

ISSN: 2639-0590



***Corresponding author:** Paul Gamboa, Departamento de Intervenciones por Cateterismo, Buenos Aires, Argentina

Submission: February 03, 2021

Published: March 19, 2021

Volume 3 - Issue 1

How to cite this article: Paul Gamboa. Takayasu's Arteritis: Etiopathogenesis and Treatment Strategies. COJ Rev & Res. 3(1). COJRR. 000552. 2021.
DOI: 10.31031/COJRR.2021.03.000552

Generalities

Takayasu's Arteritis, also known as occlusive thromboaorthopathy, occurs commonly in young women. It is pulseless vasculitis that essentially affects the aorta and its main branches, occurring more frequently in young women [1,2]. The term Takayasu disease was introduced in 1952 by Cacamise et al. [3] in honor to Dr. Mikito Takayasu, professor of ophthalmology at the University of Kanazawa in Japan, who in 1908 reported on peculiar arterio-venous anastomoses in the optic disc, caused by retinal ischemia secondary to large vessel vasculitis in a 21-year-old patient [4,5]. Later, in 1948, Shimizu and Sano detailed the clinical characteristics of the disease [6].

Although its etiology is not fully elucidated, it is accepted that genetic and infectious factors may play a role in the pathogenesis. This concept is developed in multiple investigations in the last decade. It is inferred that Takayasu's arteritis is an autoimmune disease, in which cellular immunity plays an important role, but the role of humoral immunity is still unknown. It is known that the estimulation of an antigen of an unknown nature, possibly infectious [7], would trigger the expression of heat shock proteins HSP65 (heat shock protein - 65) by the aortic tissue, activating, at the same time, the major complex class I histocompatibility, inducing Gamma-delta T cells and natural killer cells to release perforins, which results in acute inflammation. However, it is necessary to understand the humoral mechanisms responsible for this vascular damage, in order to create new management strategies, such as biological agents whose target is cytokines [8,9].

On the other hand, its prevalence varies widely in different geographic regions. For example, it is one of the main causes of renovascular hypertension in India, Korea, Japan, China and other countries in Southeast Asia [10]. In contrast, in North America atherosclerosis and fibromuscular dysplasia are the main cause of renovascular hypertension, that's why Takayasu's arteritis does not occupy a relevant place [11]. This discrepancy in the prevalence of different geographic areas, supports the idea of a genetic cause. The largest registry available up to now is in Japan with 5,881 patients affected until 2011, and a prevalence of 0.004% [12]. It has also been found that the female-male relationship varies in different countries. In Japan the ratio is 9.4: 1, while in India 1.6: 1, but it preferentially affects the female gender, which gives rise to a hormonal theory [13]. Although much of the literature that describes Takayasu's arteritis has its origin In Asia, in recent decades the recognition of patients with this disease has increased in Africa, Europe, North America and South America [14-18].

The natural history of Takayasu's Arteritis is variable and there is no pathognomonic sign of the disease. The appearance of inflammatory or systemic characteristics can precede the vascular symptoms of Takayasu's Arteritis, delaying its diagnosis for a period of time. In addition to this, many patients are studied with a diagnosis of fever of unknown origin, essential hypertension, coarctation, cardiomyopathy, or hypopituitarism before the definitive diagnosis of Takayasu's Arteritis [19]. In the acute phase of Takayasu's Arteritis, there are nonspecific symptoms such as night sweats, weight loss, and anorexia. While in the chronic phase the systemic manifestations appear according to the affected organs. Generally, patients present with claudication (upper limbs 60% vs lower limbs 30%), pulse asymmetry

(60 to 80%), and arterial hypertension. Arterial stenosis occurs three times more than aneurysm. As for them, aneurysms are more common in the aortic root which can lead to aortic insufficiency. Cardiac, renal, or central nervous system involvement can increase the morbidity and disability of the disease [20].

Diagnosis

It is important to remember that an early diagnosis coupled with timely treatment can improve the prognosis of the disease [21]. The average age for diagnosis has been found to be 28.4 years for the black population and 39.3 years for the white population [12]. The clinical characteristics of Takayasu's Arteritis described by Dr. Numano2 are:

A. Chronic vacuities that affect the intima, media and adventitia of the ascending aorta, aortic arch and its branches and the thoracic descending aorta. Most commonly in women and especially in Southeast Asia

B. Clinical presentation with local pain and signs and symptoms of regional ischemia due to stenosis or thrombosis. In rare cases it presents with rupture of vessels. When it wraps the ascending aorta, it can cause aortic insufficiency.

C. The main cause of death is renovascular hypertension.

D. Erythrocyte sedimentation rate, C-reactive protein and other inflammation markers are usually elevated. The diagnosis is confirmed through images.

E. Initial management is with high-dose steroids, maintained with low-dose steroids and aspirin. In case of poor response, immunosuppression may be required.

In 1988 Ishikawa, based on a series of 96 patients, proposed certain diagnostic criteria which were not widely accepted since it is based on the Japanese population without taking into account the different characteristics that can be found in different populations and the only mandatory criterion was being under 40 years of age, this criterion was its greatest limitation [19] since it is not fulfilled in all cases. In 1990, the American College of Rheumatology defined the diagnostic criteria for Takayasu arteritis (Table 1), being necessary to present three or more of the six criteria, with a specificity sensitivity of 90.5% and 97.8%, respectively [22]. This criterion was based on 63 patients diagnosed with Takayasu arteritis vs 744 patients with vasculitis. Despite being the most accepted criteria in the western world, it has received criticism for not taking into account coronary or pulmonary artery compromise. Furthermore, in countries where the main or only manifestation is involvement of the abdominal aorta, many patients may not be diagnosed according to these criteria.

Table 1: Criteria for the classification of Takayasu Arteritis [22].

Criteria	Definicion
Age at disease onset in year	Development of symptoms or findings related to Takayasu's arteritis at age <40 years
Claudication of extremities	Development and worsening of fatigue and discomfort in the muscles of one or more extremity with the use, especially upper extremities.
Decreased brachial arterial pulse	Decreased pulses of one or both brachial arteries.
BP in Difference>10mm Hg.	Difference of >10mmHg in systolic pressure between arms.
Bruit over subclavian arteries or aorta	Bruit audible on auscultation of one or both subclavian arteries or abdominal aorta
Arteriogram abnormality	Angiographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due arteriosclerosis, fibromuscular dysplasia, or similar causes, changes usually focal or segmental.

In 1995, Sharma et al. [23] made modifications to the Ishiwaka criteria and created new criteria for the TA diagnosis (Table 2), removed the mandatory criterion for age under 40 years, added new minor criteria such as coronary lesion in patients under 30 years of age without risk factors known. Concluding in three major criteria and ten minor criteria. The diagnosis of Takayasu's Arteritis according to Sharma would be confirmed with two major criteria or one major and two or four minors. These new criteria have a greater sensitivity of 92.5% and the same specificity 95% when comparing it with American College of Rheumatology criteria [23].

Table 2: Ishikawa criteria for modified takayasu arteritis according to Sharma et al. [23].

Major Criteria	Definition
Left mid-subclavian artery lesion	Severe stenosis or occlusion present in mid portion from 1cm proximal to the left vertebral artery origin to a 3cm distal to the origin
Right mid-subclavian artery lesion	Severe stenosis or occlusion present in mid portion from the right vertebral artery origin to point 3cm distal to the origin
Characteristic signs and symptoms of at least one months in duration.	Includes limb claudication, pulseness or pulse difference in limbs unobtainable or significant blood pressure difference (>10mmHg systolic difference in limb), fever, neck pain, Amaurosis fugax, blurred vision, syncope, dyspnea or palpitations.
Minor Criteria	Definition
Elevated erythrocyte sedimentation rate	Unexplained persistent erythrocyte sedimentation rate ESG>20mm/h (Westergren) at diagnosis or presence of evidence in the patient history

Carotodynia	Unilateral or bilateral tenderness of the common carotid artery on palpation. Must difference from neck muscle tenderness.
Hypertension	Persistence elevation of blood pressure>140/90mmHg (brachial)or>160/90mmHg (popliteal)
Aortic regurgitation or annulo-aortic ectasia	By auscultation or Doppler echocardiography or angiography
Pulmonary artery disease	Lobar or segmental artery occlusion or equivalent stenosis, aneurysm, luminal irregularity or any combination of these findings in pulmonary trunk or pulmonary arteries.
Left mid common carotid artery lesion	Severe stenosis or occlusion in the midportion, 5cm in length from a point 2cm distal to the origin
Distal brachiocephalic trunk lesion	Severe stenosis or occlusion of the distal third
Descending aortic lesion	Narrowing, dilation or aneurysm, or irregularity of the lumen or any combination of this finding involving the thoracic aorta, tortuosity alone is insufficient.
Abdominal aortic lesion	Narrowing, dilation or aneurysm, or irregularity of the lumen or combination of these finding involving the abdominal aorta; tortuosity alone is insufficient.
Coronary artery lesion	Narrowing, dilation or aneurysm, or irregularity of the lumen or combination of these finding before 30 years of age in the absence of risk factors such as hyperlipidemia or diabetes mellitus.

Regarding angiographic findings, the Nasu classification was used in the past, in which the involvement of the thoracic and abdominal aorta was not relevant. In 1996 Numano et al. [24] Found that the involvement of the descending and abdominal aorta was more common in South America and Asia with respect to Japan and created a new classification that is currently used which has five types [24]:

1. Type I: located in the supra-aortic branches of the aortic arch.
2. Type IIa: affects the ascending aorta and the aortic arch with its branches.
3. Type IIb: involvement of the ascending aorta, aortic arch with its branches and distal thoracic aorta falling.
4. Type III: includes the descending thoracic aorta, abdominal and / or renal arteries.
5. Type IV: affects the abdominal aorta and / or the renal arteries.
6. Type V: combines the findings of type IIb and IV.

Vascular abnormalities in Takayasu's Arteritis can be studied through magnetic resonance imaging, CT angiography, and ultrasound, with conventional angiography being the "Gold standard". Each method has advantages and disadvantages and should be used depending on the availability of the method and the type of patient. Conventional angiography is an invasive technique and provides less sensitivity to evaluate the widening and inflammation of the arterial wall, but it continues to be the "gold standard" for specifying and delimiting the different stenosis and occlusions. When aneurysms are present, the preferred study technique is axial tomography. Positron emission tomography promises to be as useful a tool as angiography in detecting the extent and severity of stenosis, but studies are still lacking to establish it as one of the primary tests. Although magnetic resonance imaging does not provide the same value as angiography in terms of the detail of stenosis, it is used in many cases because it is a non-invasive technique that does not involve ionizing radiation, therefore, it is the preferred technique for patient follow-up.

Differential Diagnosis

Certain congenital diseases can affect the extracellular matrix of the aorta and produce aortic insufficiency such as Marfan syndrome, Ehlers Danlos syndrome, but these conditions do not cause stenosis in the great vessels.

Treatment

Medical therapy

Corticosteroids remains the most important active treatment. Prednisolone from 0.5mg to 1mg/Kg per day is indicated for the active phase of the disease. The active phase of the disease refers to the onset or worsening of fever (in the absence of another cause), increased erythrocyte sedimentation rate, signs or symptoms of inflammation or vascular ischemia (claudication, absence of pulse) and typical angiographic lesions. Only 15% of patients do not present with active disease. The initial dose of prednisolone should be maintained for 4 to 12 weeks before starting a gradual decrease. With this management, two thirds of patients present with remission of the active phase, but more than half of these present relapses. In the event of relapses, it is recommended to increase the initial dose of prednisolone or add an immunosuppressive agent. The agents used have been methotrexate, azatrioprine, cyclosphosphamine, mycophenolate, and tacrolimus. These cytotoxic agents are usually continued for a year after remission of symptoms. There is no study that supports the choice of one of these molecules over another. Metrotexate is the most used so far, for its safety and easy handling, with an initial dose of 0.3mg/Kg / week without exceeding 15mg/week in the initial week, up to its maximum dose of 25mg/week in achieving remission upto 81% [25] and also decrease the dose of corticosteroids.

Although there is no global definition of Takayasu's Arteritis refractory on management, some studies adopt the proposal of the Takayasu's Arteritis study group from Turkey [26], which defines it as clinical or angiographic progression despite treatment with the presence of these characteristics:

a. Prednisolone greater than 7.5mg/day and use of immunosuppressive agents for more than six months.

b. New surgical interventions due to persistence of the disease

c. More than three exacerbations per year

d. Death associated with active disease.

In recent years, studies of biological agents as a management for refractory Takayasu's Arteritis have increased. The main biological agents studied have been: Inhibitor of the anti-tumor necrosis factor alpha (Etarnecep, Infliximab) as well as the monoclonal antibody (Tocilizumab), have shown a remission of up to 60% of cases of refractory Takayasu's Arteritis with the average use of 7 years and has allowed to reduce the dose of corticosteroid [27].

Surgical management

Management of patients with Takayasu's Arteritis usually includes steroids during the active phase and treatment of hypertension during the fibrotic phase. But the complications of Takayasu's Arteritis in the chronic phase are usually due to stenosis or aneurysms of the aorta and great vessels. Uncontrolled studies have been conducted comparing endovascular revascularization vs conventional surgery. These studies have proposed that the choice of revascularization therapy depends on the characteristics of the lesion, with the percutaneous technique being preferred for short lesions and difficult-to-access arteries or patients at a high risk [28]. However, the percentage of restenosis reported with both stent and balloon is approximately 71.4% at 1.3 years vs 31% at 3 years for Bypass [29,30]. Consequently, conventional surgical therapy is preferred for stenosis or occlusions in long segments, however, long-term results for bypass are not as optimal as for patients without Takayasu arteritis. There are several reasons that generate high restenosis; generally, they are long lesions, the vessels are more fibrotic, and there is a persistent state of inflation in the vessel despite clinical and laboratory improvement [29]. A report from a small center suggests that the use of a covered stent may improve restenosis due to the isolation of blood flow to the vessel walls [30].

20% of patients who present dilated ascending aorta require aortic valve replacement since the aortic regurgitation generated by the dilation can lead to left ventricular dysfunction [31]. Stenosis of the mesenteric artery and the celiac artery is usually asymptomatic, infrequent and in particular cases require surgical management. Regarding the renal artery stenosis that causes renovascular hypertension, studies have shown that long-term balloon angioplasty has similar benefits compared to surgery and stent angioplasty. Suggesting reserving stent angioplasty for cases where balloon angioplasty fails and surgery only for patients in whom angioplasty is not indicated or stent angioplasty has failed [32,33].

Conclusion

Takayasu's Arteritis is a disease of somewhat uncertain ethology due to the diversity of factors that can affect it. Its manifestations lie in the vascular condition it produces, with the aorta and its large vessels being the most affected. This vasculitis seems more prevalent in South West Asia and despite having been described for several years in Europe and America, only series of cases have been reported, which could indicate a possible under-diagnosis. Knowledge of this vasculitis is important since its timely management can prevent the progression of the disease and the presentation of vascular complications. The management of a patient with Takayasu's Arteritis will continue to be a challenge for clinicians, since there are no single standard and management decisions are generally based on the recommendation of experts, so each case must be individualized to offer the most appropriate therapy and reduce the occurrence of complications.

References

1. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, et al. (1994) Takyasu arteritis. Ann Intern Med 120(11): 919-929.
2. Numano F, Okawara M, Inomata H, Kobayashi Y (2000) Takayasu's arteritis. Lancet 356(9234): 1023-1025.
3. Caccamise WC, Whitman JF (1952) Puleseless disease: A preliminary case report. Am Heart J 44(4): 629-633.
4. Numano F, Kakuta T (1996) Takayasu arteritis five doctors in the history of Takayasu arteritis. Int J Cardiol 54(Suppl): 1-10.
5. (1908) Takayasu M: A case of a peculiar change in the central retinal vessels. Acta Soc Ophthalmol Jpn 12: 554.
6. Shimizu K, Sano K (1951) Pulseless disease. J Neuropathol Clin 1(1): 37-47.
7. Arun R (2015) Analysis of evidence to determine the link between Takayasu's arteritis and Tuberculosis. Indian Journal of Rheumatology 10(1): 2-9.
8. Arnaud L (2011) Pathogenesis of Takayasu's arteritis: A 2011 update. Autoimmunity Reviews 11(1): 61-67.
9. Arnaud L (2006) Takayasu's arteritis: An update on physiopathology. Eu J Int Med 17(4): 241-246.
10. Sharma BK, Sagar S, Chugh KS, Sakhuja V, Rajachandran A, et al. (1985) Spectrum of renovascular hypertension in the young in North India: A hospital-based study on occurrence arid clinical features. Angiology 36(6): 370-378.
11. Maxwell MH, Bleifer KH, Frauklin SS, Varady PD (1972) Cooperative study of renovascular hypertension: Demographic analysis of the study. J Am Med Assoc 220(9): 1195-1204.
12. Alibaz-Oner F, Direskeneli H (2015) Update on Takayasu's arteritis. Presse Med 44: e259-e265.
13. Sharma S (1998) A possible role of sex in determining distribution of lesions in Takayasu Arteritis. Int J Cardiol 66(Suppl 1): S81-S84.
14. Cañas CA, Jimenez CA, Ramirez LA, Uribe O, Tobón I, et al. (1998) Takayasu arteritis in Colombia. Int J Cardiol 66 (Suppl 1): S73-S79.
15. Dufrechou CA, Cedrés SA (2006) Arteritis de Takayasu. Rev Med Urug 22: 236-240.
16. Dabague J, Reyes Pedro A (1996) Takayasu arteritis in Mexico: A 38-year clinical perspective through literature review. Int J Cardiol 54 (Suppl): 103-109.
17. Buzaid AC, Milani JR, Calich Y, Pereira VG (1985) Arterite de Takayasu: estudo de 16 casos, aspectos clinicos, laboratoriais, e revis, oda literatura. Rev Assoc Md Bras 3(5-6): 85-90.
18. López M, Gonzalez P, Esther N (1987) Takayasu's arteritis in Puerto rico: A clinical study. Bol Asoc Md PR 79: 230-235.

19. Ishikawa K (1988) Diagnostic approach and proposed criteria for the clinical diagnosis of Takayasu's arteriopathy. J Am Coli Cardiol 12(4): 964-972.

20. Sharma B (1996) Diagnostic criteria for Takayasu arteritis. International Journal of Cardiology 54 (Suppl) : S127-S133.

21. Maksimowicz K, Gary SH (2007) Takayasu arteritis: What is the long-term prognosis? Rheum Dis Clin N Am 33(4): 777-786.

22. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, et al. (1990) The American college of rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 33(8):1129-1134.

23. Sharma BK, Iliskovic NS, Singal PK (1995) Takayasu arteritis may be underdiagnosed in North America. Can J Cardiol 11(4): 311-316.

24. Hata A, Noda M, Moriwaki R, Numano F (1996) Angiographic findings of Takayasu arteritis: New classification. Int J Cardiol 54(Suppl): 155-163.

25. Hoffman GS, Leavitt RY, Kerr GS, Rottem M, Sneller MC, et al. (1994) Treatment of glucocorticoid resistant or relapsing Takayasu arteritis with methotrexate. Arthritis Rheum 37(4): 578-582.

26. Saruhan-Direskeneli G, Travis H, Kenan A, Gokhan K, Patrick C, et al. (2013) Identification of multiple genetic susceptibility loci in Takayasu arteritis. Am J Hum Genet 93(2): 298e-305e.

27. Hoffman GS, Merkel PA, Richard D, Deborah J, Patrick L (2004) Anti-tumour necrosis factor therapy in patients with difficult to treat Takayasu arteritis. Arthritis Rheum 50(7): 2296-2304.

28. Sharma S, Gupta H, Saxena A, Kothari SS, Taneja K, et al. (1998) Results of renal angioplasty in nonspecific aortoarteritis (Takayasu disease). J Vasc Intev Radiol 9(3): 429-435.

29. Keser G, Direskeneli H, Aksu K (2011) Management of Takayasu arteritis: a systematic review. Rheumatology 53(5):793-801.

30. Qureshi MA, Martin Z, Greenberg RK (2011) Endovascular management of patients with Takayasu arteritis: stents versus stent grafts. Semin Vasc Surg 24(1): 44-52.

31. Zhang Y, Fan P, Zhang H, Wenjun M, Lei Song, et al. (2019) Surgical treatment in patients with aortic regurgitation due to Takayasu arteritis. Ann Thorac Surg 110(1): 165-171.

32. Kinio H, Kafa AT (2015) The results of treatment in renal artery stenosis due to Takayasu disease: Comparison between surgery, angioplasty, and stenting. A monocentrique retrospective study. Giornale di Cirugía 36(4): 161-167.

33. Ambrish S, Debashish D, Salman H, Abul KN, Ashish M, et al. (2020) Efficacy and safety of tocilizumab in treatment of Takayasu arteritis: A systematic review of randomized controlled trials. Modern Rheumatology 31(1): 197-204.