An Overview of Takayasu Arteritis at an Academic Hospital in Central South Africa

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Acknowledgement and dedication:

I would like to acknowledge my friends and family in supporting me during the writing of this project and dedicate this to my late father Dr JJ Botha who has always inspired me to follow in his footsteps and become a good clinician.

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Executive summary

Purpose of the study Takayasu arteritis (TA) is a chronic granulomatous inflammatory vasculitis of large and medium vessels of unknown aetiology. It has a predilection for the aorta and its branches, and can affect the brachiocephalic, carotid, subclavian, vertebral, and renal arteries, as well as the coronary and pulmonary arteries. Expression of the disease is variable, often leading to symptoms of ischaemia due to blood vessel stenosis or thrombus formation within a vessel. An unknown, yet identified antigen, is thought to initiate an autoimmunological response in a genetically susceptible patient, where mononuclear infiltration in the vasa media leads to granulomatous inflammation resulting in medial thickening, intimal proliferation and obliteration of elastic layers and medial smooth muscles with cellular infiltration around the vasa vasorum.

Disease progression causes tunica media destruction, often with resultant aneurismal formation or acute aneurismal dissection of affected arteries. The epidemiological distribution of TA is worldwide with the highest prevalence occurring in the Asian population. The disease is more prevalent in younger females with a female to male ratio of 4-9: 1. TA may show heterogeneous disease expression, patterns of arterial involvement and prognosis in different parts of the world. Available data on the African continent and specifically South Africa is limited. The largest study on adults with TA in SA was done in the Western Cape Province at Groote Schuur Hospital. Case reports have been documented in South Africa and Africa. Published literature in South Africa mainly has been focused on TA in the paediatric population group, and, in the Free State Province of South Africa, no published literature has been found. Clinical manifestations are variable, ranging from initially asymptomatic to vague and non-specific symptoms. As the disease progresses, classical features of TA begin to emerge with ischemic symptoms being a prominent feature. The classification of TA requires at least three of the six criteria of the American College of Rheumatology of 1990 to be present. There is often a delay in the diagnosis due to non-specific symptoms and variable clinical presentation.

The diagnosis is often missed due to low clinical awareness and suspicion. No standardized criteria to assess disease activity have been formalized, further contributing to the difficulty in managing the disease. Thus far, no definitive biomarker has been found to diagnose TA. Imaging is paramount to making the diagnosis, establishing the extent of arterial involvement, and assessing disease progression and response to treatment. Computerised tomography angiography (CTA) or magnetic resonance angiography (MRA) is used to establish the diagnosis of TA. CTA is most often used in our setting due to restrictions to the accessibility of MRI. CTA and MRA are beneficial for the assessing the aorta and its main branches. Treatment for TA can be subdivided into medical and surgical treatment. The ultimate goal of treatment is to suppress the vascular inflammatory process. The natural history and prognosis of TA remains poorly defined. This is due to lacking data for long term follow up. Prognosis mainly depends on the development of complications, albeit from the disease itself or as a consequence of medical or surgical treatment. Further important prognostic factors are duration and extent of both vascular and systemic inflammation, late presentation and diagnosis and treatment resistance.

Methods Patients who met the 1990 American College of Rheumatology criteria for the diagnosis of TA were included in this retrospective study over a twenty-one-year study

period from 2000 until 2021. This study comprised of adult and paediatric patients seen at Universitas Academic Hospital, in the city of Bloemfontein, Free State. They were referred to Universitas Academic Hospital, which is a tertiary institution, from other centrally located hospital in South Africa.

The records of patients were reviewed, and data were analysed from the departments Rheumatology, Vascular Surgery and Paediatrics. This included patient demographics (sex, age, and ethnicity), 1990 ACR criteria, clinical features, anatomical classification, surgical interventions, medical treatment, response to therapy, complications, and outcome. Patients were excluded if there were missing data on clinical features, if no imaging studies were performed and if they had an alternate diagnosis.

Key results The mean age at presentation was fourteen years (9-23), with 71.8% (n= 28) female patients, and this correlates with previous studies on sex predominance and age characteristics. The cohort constituted of 71.8% (n=28) patients of Black African ethnicity and 28.2% (n=11) patients of coloured ethnicity. There were no patients of white, Indian, or Asian ethnicities included. The most common clinical features at presentation were cardiac disease (61.5%, n=24), hypertension (56.4%, n=22) and cerebrovascular disease (48.7%, n=19). 17.9% (n=7) and 15.8% (n=6) of patients presented with peripheral vascular disease and constitutional symptoms, respectively. Gastrointestinal, respiratory, and dermatological manifestations were only present in 5.1% (n=2), respectively. Angiography demonstrated the abdominal aorta to be the most frequently involvement (71.8%, 28/39), followed by common carotid artery lesions (58.9%, 23/39), subclavian artery lesions (56.4%, 22/39) and thoracic aorta lesions (48.7%, 19/39). Therefore, Numano type IV was most commonly found in this study followed by Numano type I and type IIa. Type III and Type IIb was the least common. Stenotic lesions were more common than aneurysmal disease. 94.7% (n=36) of patients were treated with glucocorticoids (GCs). 68.4% (n=26) were combined with Methotrexate and 23.7% (n=9) with Azathioprine. 31,6% (n=12) received Cyclophosphamide 2.6% (n=1) were treated with Mycophenolate Mofetil (MMF). No patients were treated with biologics. Surgical interventions comprised mainly of open surgical procedures.

Conclusions This study revealed that TA, which is a large vessel vasculitis, remains rare, and improving awareness is important for making an early diagnosis and preventing morbidity and mortality. The aetiology remains uncertain although an autoimmune process is implicated. Demographical data and clinical features remain comparable to previous studies worldwide and in previously done South African studies. Cardiovascular and cerebrovascular manifestations were the most frequently seen and lead to significant morbidity. Immunosuppression remains the mainstay of treatment with all patients on glucocorticoids during the course of treatment. Glucocorticoids were still heavily relied upon in the treatment of these patients.

Recommendations Future studies can be done to focus on ways in identifying patients with Takayasu arteritis earlier and exploring to identify novel biomarkers for use in diagnosis and disease activity assessment. Future research on individuals who were treated with biologics earlier in the course of their disease will be crucial to making improvements in the management of this difficult disease and comparing their outcome with patients on conventional disease modifying agents.

Keywords

Takayasu arteritis; vasculitis; granulomatous inflammation; young female; clinical and radiographic findings

List of abbreviations

- ACR = American College of Rheumatology
- AECA= Anti-epithelial cell antibodies
- AZA = azathioprine
- CDU=colour Doppler ultrasonography
- CRP =C- Reactive Protein
- CTA = computer tomography angiography
- CYC = cyclophosphamide
- DEI TAK= Disease extent index in Takayasu arteritis
- ESR = erythrocyte sedimentation rate
- FDG-PET/CT= Fludeoxyglucose positron emission tomography
- GC= Glucocorticosteroids
- GCA = Giant cell arteritis
- HLA = Human leukocyte antigens
- LEF = leflunomide
- MHC = Major Histocompatibility Complex
- MMF = mycophenolate mofetil
- MRA = magnetic resonance angiography
- MTX = methotrexate
- NK cells = natural killer cells
- PDGF = platelet-derived growth factor
- TCZ= Tocilizumab
- TNF = Tumor necrosis factor
- VEGF = vascular endothelial growth factor
- TA = Takayasu arteritis

- TIA= transient ischaemic attack
- TB = tuberculosis

Chapter 1

Literature review

Background and History of Takayasu arteritis

Earliest published data about TA dates back as far as 1830. Mikito Takayasu, Ophthalmologist at Kanazawa University in Japan, presented the clinical scenario of a woman with distinct abnormal retinal vascular findings in 1908 (1). Thereafter, Takayasu's colleagues, Katsutomo Ohishi, and Tsurukichi Kagoshima, in a later academic discussion, described the more typical cases of patients with absent pulses (1)(2)(3).

In 1939, Yasuzo Shinmi, coined the term 'Takayasu's Arteritis'(TA), after more cases were reported in Japan. Then in 1951, surgeons at Tokyo University, Kentaro Shimizu and Keiji Sano, introduced TA to the Western world as pulseless disease. A publication on TA by Whiteman and Caccamize in the American Heart Journal, in 1952, led to the dispersal of knowledge on TA into Western nations (4).

Internists, Ross and McKusick, outlined over 100 cases where decreased or absent pulses in the arms and neck were found, and called this disease entity 'aortic arch syndrome'. They recognised the cases according to the cause of disease as either syphilitic, congenital abnormality, atherosclerotic or traumatic. They cited four cases in their case series as 'young female arteritis', noting these patients as having characteristic ocular and cerebral vascular findings (4).

In 1963, Professor Hideo Ueda, Internist at Tokyo University, studied cases of TA and confirmed pan aortitis involving the aorta and its main branches and referred to it as 'pan aortitis syndrome'. Professor Ueda postulated an autoimmune aetiology and later renamed it 'aortitis syndrome' to avoid confusion of involvement of the whole aorta (4). In 1975, in honour and recognition of Takayasu as first reporting the disease entity, the Department of Health and Welfare in Japan's research committee proposed naming the disease 'Takayasu Arteritis' (4).

Introduction

The different group of systemic inflammatory illnesses known as vasculitides is characterised by inflammation and, consequently, blood vessel destruction. This ultimately results in ischemia and damage to the tissues or organ supplied by the affected blood vessels.

Any type, size or site of blood vessel may be involved. Vasculitis can be primary/idiopathic or secondary due to another underlying disease. The inflammation can be limited to a single organ, or it can affect multiple organs concurrently. The size of the affected blood vessel classifies the vasculitides into large-vessel vasculitis, medium-vessel, and small-vessel vasculitis. Available literature on TA focuses on describing the clinical features and management of the disease. These prior studies highlight that TA is still of unknown aetiology with often late and advanced presentation. Most of the data originates from Asia with sparse data available on a sub-Saharan population and specifically South Africa (5). No data are available about TA in the Free State.

Multiple authors have attempted to correlate the pattern of disease involvement to their population demographic (2)(5)(6). Variation in pattern of disease has been demonstrated in some studies, with comparative study showing Japanese patients having disease more frequently of the aorta arch and its branches than Korean and Indian patients who had disease of the abdominal aorta (7).

TB (tuberculosis) has been postulated as a possible aetiology, which is of particular interest in the South African context, keeping in mind the high burden of disease in South Africa (8)(9). It is difficult to establish a causal relationship between TB and TA. With high prevalence of TB in South Africa, the implication may be an incidence higher to other countries where TB is not endemic, which has not been established.

Definition

Takayasu arteritis (TA) is a chronic granulomatous inflammatory vasculitis of large and medium vessels of unknown aetiology (6)(10). It has a predilection for the aorta and its primary branches including the brachiocephalic, carotid, subclavian, vertebral, and renal arteries, in addition to occasionally affecting the coronary and pulmonary arteries. Expression of the disease is variable, often leading to symptoms of ischaemia due to blood vessel stenosis or thrombus formation within a vessel. Disease progression causes tunica media destruction, often with resultant aneurismal formation or acute aneurismal dissection of affected arteries.

Characterised histologically as 'pan-arteritis', resulting in intimal thickening, obliteration of medial elastic layers and medial smooth muscles, inflammatory cellular infiltration in the media with infiltration around the vasa vasorum.

Epidemiology

TA is distributed world-wide, with the Asian population experiencing the highest prevalence. The disease is more prevalent in younger females with a female to male ratio of 4-9: 1. The incidence in Asian countries is reported as 1 to 2 cases/million per year and an estimated prevalence of 12.9 to 40 cases/million (3).

TA may exhibit heterogeneous disease expression, patterns of vascular involvement and prognosis around the world (11) (12). In contrast to Asia, the incidence has been reported as 0.3 cases/million in the United Kingdom (13). Epidemiologic studies have concluded that TA has been diagnosed in European countries with increasing prevalence, with a reported incidence rate between 0.4 to 1.5 per million (14).

Available data on the African continent and specifically South Africa is limited. The largest study on adults with TA in SA was done in the Western Cape Province at Groote Schuur Hospital. This was a retrospective, descriptive study spanning over 50 years and included 272 patients (15).

Case reports have been documented in South Africa and Africa (16). Published literature in South Africa mainly has been focused on TA in the paediatric population group, and, in the Free State Province of South Africa, no published literature has been found.

Clinical presentation

Clinical manifestations are variable, ranging from initially asymptomatic to vague and non-specific symptoms, to limb claudication, systemic and renovascular hypertension to cerebrovascular accidents.

Non-specific symptoms include fever, malaise, weight loss, myalgia, or arthralgia. As the disease progresses, classical features of TA begin to emerge with ischemic symptoms being a prominent feature. Hypertension due to stenosis of the aorta or renal artery is a common presentation.

The following are disease features (17):

• Constitutional symptoms: fever, weight loss and fatigue – common in early phase of the disease.

• Arthralgia/ Myalgia: intermittent or continuous and chronic in nature.

• Carotidynia: tenderness on palpation of a carotid artery in 10 to 30 percent of patients.

• Absent or weak peripheral pulse(s): most common at radial arteries and is often asymmetric; unusual cases of acute vessel occlusion occur with limb gangrene or ischemic ulcerations; however, this is uncommon due to the usual formation of collateral circulation indicating the chronic nature of disease development.

• Claudication: limb claudication is a common presenting symptom. Subclavian steal syndrome can lead to neurological symptoms or syncope related to exercise induced redirection of blood flow to the upper limb. This results from a stenotic lesion proximal to the origin of the vertebral artery. Other symptoms of claudication include mild to severe upper- or lower limb pain with activity often causing functional impairment.

• Arterial bruit: in patients with stenotic lesions, bruits are audible over the stenosed vessels. Signs and symptoms of aortic stenosis or aortic incompetence can also be present with resultant heart failure in some cases.

• Blood pressure discrepancy between the arms.

• Hypertension: due to coartation of the aorta or renal artery stenosis.

• Angina pectoris: myocardial ischemia can occur due to stenosis of the coronary artery ostia from aortitis or coronary artery inflammation with coronary arteritis. This can lead to myocardial infarction and in complications related to myocardial infarction including mechanical complications (free wall rupture of the left ventricle, interventricular septum rupture, secondary severe mitral regurgitation); pericardial complications; conduction abnormalities; left ventricular dysfunction and left ventricular aneurysm.

• Mesenteric artery ischemia with involvement of abdominal aorta causing post-prandial pain, diarrhoea, and gastrointestinal haemorrhage.

• Skin lesions resembling pyoderma gangrenosum or erythema nodosum.

• Neurological involvement: involvement of the vertebral and carotid arteries with sequelae of decreased cerebral blood flow- dizziness, syncope, transient ischaemic attack, and stroke. A late manifestation of severe disease is visual impairment.

• Respiratory manifestations include dyspnoea, chest pain, haemoptysis, and pulmonary hypertension.

Diagnosis

Takayasu arteritis classification requires that three of the six criteria of the American College of Rheumatology of 1990 be present. The ACR criteria for TA are:

1. Age of onset before 40 years old.

2. Limb claudication.

3. Reduced pulse in the brachial artery.

4. A systolic pressure difference of more than 10 mmHg between two limbs.

5. A bruit in the aorta or subclavian arteries.

6. Angiographic evidence of narrowing or occlusion of the aorta, its primary branches, or large arteries in the proximal upper or lower extremities.

• The sensitivity and specificity of three of more of these six criteria are respectively 90.5% and 97.8% (6).

• Non-specific symptoms often predominate, especially early on in the course of the disease, as well as variability in clinical presentation and this delays making the correct diagnosis
(18).

• The diagnosis is often missed due to low clinical awareness and suspicion (5). No standardized criteria to assess disease activity have been formalized, further contributing to the difficulty in managing the disease. Thus far, no definitive biomarker has been found to diagnose TA (5). Imaging is paramount to making the diagnosis, establishing the degree of arterial involvement, and assessing disease progression and response to treatment (19).

• There is poor correlation between systemic markers of inflammation and inflammation in the vessel wall. There may be active inflammation without elevation of markers of inflammation such as ESR or CRP, and the converse applies. Histological evaluation of arterial specimens of patients in clinical and laboratory remission, may show signs of inflammation. According to the Numano classification, TA is classified into six different subtypes, based on radiographical vascular involvement (5).

• The diagnosis is infrequently made histologically since biopsy of large vessels is impractical (11). However, the diagnosis can be made when an arterial biopsy is available after a revascularizing procedure or repair of an aneurysm.

Assessment of Disease Activity

Disease activity assessment is vital in managing autoimmune diseases. Clinical assessment of disease activity in TA is based on clinical findings, inflammatory markers, and imaging studies (48). Assessing active disease is a challenging task in TA. Unlike other autoimmune diseases, for example rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), where the area of disease is accessible for biopsy, this is not the case for TA. This is due to the inability to obtain a histopathological diagnosis, except in case of vascular biopsy during bypass surgery. Disease extent is extrapolated from the DEI TAK (Disease extent index in Takayasu arteritis) tool, which is a validated tool developed by Indian Rheumatology Association Core Group for Vasculitis (IRVAS), derived from the Birmingham Vasculitis Activity Score (BVAS). The DEI TAK score uses clinical findings in assessing the extent of disease (47).

Imaging modalities used for diagnosis and follow-up:

Computerized tomography angiography (CTA) or magnetic resonance angiography (MRA) is used to confirm the diagnosis of TA. CTA is most often used in our setting due to restrictions to the accessibility of MRA. CTA and MRA are helpful for the evaluation of the aorta and its main branches. The aorta's structural alterations may be well-characterized anatomically by CTA, but it may not identify early disease activity. Although MRA can demonstrate thickening of the artery walls, oedema, and contrast enhancement, it has been demonstrated that there is little association with clinical activity or systemic inflammation and that its utility for long-term follow-up is limited (12).

Similarly, Colour Doppler Ultrasonography (CDU) is useful for assessing the femoral, axillary, carotid, and temoral arteries, but it does not reflect the thoracic aorta unless it is performed via transoesophageal examination. Similar to CTA and MRA, CDU can detect stenoses, aneurysms, and major artery luminal abnormalities in addition to the characteristic homogenously thickened vessel walls, mural inflammation, and oedema, which are early signs of inflammation. In addition, CDU offers superior resolution to CTA and MRA. Radiation exposure does not limit the use of MRA or CDU. The overestimation of arterial occlusions, difficulty visualising small branch arteries, and vascular calcifications are all limitations of MRA (12).

The non-invasive imaging technique of positron emission tomography (PET) using 18F-fluorodeoxyglucose (18F-FDG PET) analyses 18F-FDG, which accumulates in hyper-metabolic, activated inflammatory cells infiltrating the arteries. The functional data from PET and the anatomical data from CT are combined in 18F-FDG PET/CT. The most accurate diagnosis for early vascular inflammation is 18-FDG-PET (12). Thus, employing PET-CT in the first two phases may allow for the detection of early vascular inflammation as well as the location of such inflammation in the aorta and its branches, which may aid in the early diagnosis of TA. Although it may be difficult to distinguish between atherosclerotic and vasculitic lesions, PET vascular uptake is not vasculitis specific. However, PET cannot distinguish between arterial wall structure and luminal flow; a further drawback of PET-CT imaging is the substantial radiation dose (12).

The Numano classification classifies the disease into 6 types based on radiographic involvement:

Type 1: Branches from aortic arch

Type 2a: Ascending aorta, aorta arch and its branches

Type 2b: Ascending aorta, aortic arch, its branches and descending thoracic aorta

Type 3: Thoracic descending aorta, abdominal aorta and or renal arteries

Type 4: Abdominal aorta and or renal arteries

Type 5: Combined features of 3 and 4.

Differential diagnosis includes:

- Other primary vasculitides (Kawasaki's disease, Polyarteritis Nodosum and Buerger's disease).
- Atherosclerosis and arteriolosclerosis
- Hypercoagulable states (thrombotic thrombocytopenic purpura, antiphospholipid syndrome)
- Congenital (aortic coartation, middle aortic syndrome)
- Vasospastic disorders (posterior reversible encephalopathy syndrome and reversible cerebral vasoconstriction syndrome)
- Infectious causes (cytomegalovirus, herpes virus, hepatitis viruses, HIV, tuberculosis, syphilis, Staphylococcus aureus)
- Malignancies (leukaemia, lymphoma, glioma)
- Immunodeficiency disorders
- Iatrogenic (post radiation therapy)
- Autoimmune secondary vasculitis (SLE, sarcoidosis)
- Renal disorders
- Drugs (cocaine, sympathomimetics)
- Livedoid vasculopathy
- Inherited disorders (Marfan's syndrome, Ehlers-Danlos, neurofibromatosis type I)
- Fibromuscular dysplasia

Pathogenesis

Although the exact aetiology of TA is unknown, the underlying pathology is inflammatory in nature with possible underlying autoimmune disease. This is supported by the finding of elevated levels of cytokines in the sera of patients with TA (45). The antigen or antigens that could trigger the autoimmunity have not been identified yet, however, it has been postulated that a viral or bacterial antigen initiates or produces, through molecular mimicry, the autoimmune process in TA (45). The concept of the "vascular microbiome" has been known for some time, where commensal microorganisms in the blood vessels of healthy patients differ from those of patients with pathological vasculature and vasculitides. Therefore, alteration in the vascular microbiome, called "dysbiosis" could lead to the pathogenesis of

TA (46). The disease is characterised by pan-mural involvement with cellular infiltration and intimal proliferation. Activation of vasa vasorum endothelial cells and recruitment of lymphocytes is involved in the pathological process of TA (34).

Natural killer (NK) cells, macrophages, neutrophils, CD4+ T cells, CD8+ T cells, T cells, and inflammatory cells invade the vasa vasorum (10) (20). T-cells, NK cells, and macrophages are the primary drivers of TNF-α production. TNF-α plays an essential part in the formation of granulomas (21) (22). By producing perforin and the killer cell lectin-like receptor subfamily K (NKG2D), T- and NK cells are involved in the death of endothelial cells, according to histopathological analysis of samples of aortic tissues (23).

Acute inflammation results from the release of perforin and other mediators by T and NK cells that express NKG2D receptors upon recognizing MHC1A (the major histocompatibility class I chain-related A) on vascular smooth muscle cells. The natural killer and T-cells also release pro-inflammatory cytokines, which stimulate the production of matrix metalloproteinase (MMPs) and enhance the inflammatory response. The major histocompatibility complex (MHC) antigen increases as a result, and more mononuclear cells are attracted into the vascular wall. Patients with TA were observed to have peripheral T-cells that were active and had a higher CD4/CD8 ratio, indicating that T-helper cells predominated in these patients (24).

Th1 lymphocytes produce interferon-γ, which activates macrophages and causes the release of vascular endothelial growth factor (VEGF), resulting in the formation of giant cells. Increased neovascularization and platelet-derived growth factor (PDGF) release are brought on by VEGF. Smooth muscle migration into the intima and intimal proliferation are the process's ultimate endpoints. By the stimulation of invading neutrophils, Th17 cells produced by the IL-23 milieu also contribute to vascular lesions (25). The contribution of TA pathogenesis by B-cells is still debated.

Patients with TA have reportedly been shown to have anti-aorta antibodies and anti-epithelial cell antibodies (AECA) (26). Systemic vasculitis constitutes only one of the clinical diseases where AECAs have been found. There is an abundance of data to suggest that AECAs cause vasculitis, activate endothelial cells, and cause apoptosis (27). Moreover, it has been reported that TA patients frequently exhibit antiphospholipid antibodies, particularly those against cardiolipin, annexin V, and 2 glycoprotein I. (28). It is still unknown if these antibodies contribute to the pathogenesis of TA.

Other antibodies found in the sera of TA patients include anti-human heat shock protein60/65 autoantibodies (29). None of these, however, have demonstrated specificity to TA. IL-6, IL-8, IL-16, and IL-18 levels have been found to be increased in TA patients, and IL-18 and IL-16 levels are positively correlated with disease activity (30). The correlation between TA and HLA alleles raises the possibility that genetic factors contribute to the aetiology of TA. HLA-B*52 is the only gene that exhibits an association with TA outside ethnicity, according to an analysis of these genetic factors within as well as outside the HLA domain (31).

Two separate susceptibility loci within the HLA region, HLA-DQB1/HLA-DRB1 and HLA-LAB/MICA, have been found and confirmed by a recent large-scale genetic association study that included patients from Turkey, North America and Europe. This study found that patients from North America and Europe similarly had a connection between TA and HLA-

B*52 (32). Recent studies have revealed that TA has a number of non-HLA susceptibility loci (14).

Treatment

Treatment for TA can be subdivided into medical and surgical treatment. The ultimate goal of treatment is to suppress the vascular inflammatory process. In cases with life-threatening arterial stenosis or marked aneurysmal formation, open surgical procedures or endovascular procedures are further treatment options to be considered. As a general rule, surgical interventions should only be performed after suppression of inflammation by appropriate and adequate medical therapy (33). Therefore, to optimally treat TA, adequate assessment of disease activity by clinical and radiological evaluation should be performed.

The EULAR consensus definition of active disease is as follows:

1) The presence of typical signs or symptoms of active LVV (large vessel vasculitis).

2) Additionally, at least one of the following:

a. Active inflammation on imaging or tissue biopsy.

b. LVV ischaemic complications.

c. Persistently elevated inflammatory markers (other causes excluded (34).

Medical treatment

Glucocorticosteroids (GC) form the cornerstone of initial immunosuppressive (IS) therapy. Conventional second line treatment consists of Methotrexate, Mycophenolate mofetil, Leflunomide and Azathioprine, as monotherapy or combined with GC to enable tapering of the GC dose.

Cyclophosphamide is also an option but is usually reserved for severe or refractory cases, due to the well-known long term adverse effects such as gonadal suppression.

Although there are no universally accepted criteria for the definition of refractory disease in TA, the Turkish Takayasu Arteritis Study Group definition is used to define refractory disease (35):

1. Disease progression despite treatment based on clinical and radiographical evaluation

2. Any of the following characteristics:

• Prednisone dose >7.5 mg/day after 6 months of treatment, despite administration of conventional IS agents.

• Persistent disease activity requiring surgery.

• ≥ Three attacks per year.

• Death due to active disease; and

• In cases of refractory disease, biological agents such as Rituximab, Tocilizumab, TNF inhibitors and Abatacept can be used. Evidence from observational studies have

shown that biological agents are effective in refractory cases or in cases with disease progression (36).

Surgical treatment

In the late presentation and chronic phases of TA, where vascular lesions are irreversible with medical treatment alone, surgery or endovascular interventions may be considered.

In cases of severe ischemic symptoms of an extremity or severe ischemia to an organ, revascularisation by either endovascular or open surgical intervention may be necessary.

Important indications for surgery are symptomatic cerebral artery stenosis causing cerebrovascular ischemia; coronary artery ischemia; abdominal aorta aneurysm and aortic bifurcation disease with lower limb claudication and ischemia; hypertension caused by renal artery stenosis; severe aortic regurgitation and severe stenosis of the aorta arch (37)(38)(39)(40).

Pregnancy and Fertility

Obstetric complications are more common in women with TA (49). Pre-conception counselling and planning is therefore imperative for a favourable pregnancy outcome. Pregnancy is generally not associated with disease progression, nevertheless, pregnant patients should be managed in a high-risk maternal unit. Complications posing maternal risk are attributable to systemic hypertension leading to the development of complications such as pre-eclampsia, worsening of chronic hypertension, heart failure and strokes. Foetal complications such as growth restriction are because of impaired placental blood flow secondary to uncontrolled hypertension and involvement of the abdominal aorta. Another reason for growth restriction is stenosis of the renal arteries with increased production of renin, causing increased blood pressure (41). Fertility is not directly affected by TA; however, counselling about the risks of teratogenicity of certain immunosuppressive drugs is necessary (41).

Complications and Prognosis

The natural history and prognosis of TA remains poorly defined. This is due to paucity of data for long term follow up. Prognosis depends on the development of complications, albeit from the disease itself, or because of medical or surgical treatment. Further important prognostic factors are severity and extent of systemic and vascular inflammation, late presentation and diagnosis and treatment resistance (4).

Other contributors to poor prognosis include aortic regurgitation , aortic aneurysm, the presence of renal artery stenosis with renovascular hypertension, Takayasu retinopathy, and co-morbidities as a consequence of corticosteroid treatment (4). Hypertension as well as accelerated atherosclerosis due to chronic inflammation are important complications which need early identification and treatment (42). An important complication post-surgery is in-stent stenosis (43).

Progressive vessel wall fibrosis and calcification resulting in external stent compression, has been postulated to contribute to this complication.

Mortality in patients with TA are usually related to strokes, aneurysm rupture, myocardial infarction, renal failure and cardiac failure (44).

Aim

This single centre, retrospective study aims to provide data on TA which has largely been undocumented in South Africa, with no existing data in the Free State. This study will provide a valuable contribution to the description of TA in the Free State province.

Objectives

To describe the clinical-, radiographical features and treatment of patients with TA at Universitas Academic Hospital in the Free State province of South Africa.

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Chapter 2

An Overview of Takayasu Arteritis at an Academic Hospital in Central South Africa

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Abstract

Background

Takayasu arteritis (TA) is a rare chronic granulomatous inflammatory vasculitis of large- and medium, usually involving the aorta and its main branches (the carotid, subclavian, brachiocephalic, vertebral, and renal arteries). The disease aetiology remains unknown, although it is presumed to be an autoimmune disease, and leads to vascular damage in the form of stenosis or aneurysmal dilatation. It is more common in younger females and in certain ethnic groups. It has a heterogeneous clinical presentation, making awareness and high index of suspicion imperative in making the diagnosis. Angiography remains the primary diagnostic tool in TA as laboratory tests are non-specific and do not always correlate with active inflammation. TA can be subdivided into six types based on angiographic findings. Immunosuppression with steroids or steroid-sparing therapies remain the cornerstone of therapy. Indications for surgery are in cases of life-threatening end-organ ischaemia or where progressive disease is present despite adequate medical therapy.

Aim

This single centre, retrospective study aims to provide data on TA which has largely been undocumented in South Africa, with no existing data in the Free State. This study will provide a valuable contribution to the description of TA in the Free State province.

Objectives

To describe the clinical-, radiographical features and treatment of patients with TA at Universitas Academic Hospital in the Free State province of South Africa.

Methods

Study design

This was a retrospective, descriptive study done over a 21-year period at Universitas Academic Hospital in Bloemfontein in the Free State province of South Africa. Universitas Academic Hospital provides a tertiary service to patients from the Free State as well as other centrally located provinces, including the Northern Cape and the Eastern Cape as well as the neighbouring country of Lesotho.

Number of participants

A total number of 39 patients with Takayasu Arteritis were identified and included.

Study population

This study comprised of adult and paediatric patients seen at Universitas Academic Hospital, that fulfil the American College of Rheumatology 1990 criteria for Takayasu Arteritis. Patients were referred to Universitas Academic Hospital from other centrally located hospitals in South Africa.

Inclusion criteria

Fulfil ACR 1990 criteria for Takayasu Arteritis. Seen at Universitas Academic Hospital Rheumatology, Vascular surgery, or Paediatric divisions.

Exclusion criteria

Missing data on clinical features or CT angiography not performed. Uncertainty of diagnosis or disease due to secondary causes.

Ethical considerations

Ethical approval was obtained from the Health Sciences Research Ethics Committee with approval number **UFS-HSD2022/0116/2908**.

Results

Thirty-nine patients with Takayasu arteritis were identified. The medical records of these thirty-nine identified patients were reviewed. Most patients were female (71.8 % n= 28). 71.8 % of patients were of Black African ethnicity (n= 28) and 28.2% (n= 11) were coloured. Median age at presentation was fourteen years (IQR 9,23), all participants were less than forty years old. Twenty-four patients (61.5 % n=24) presented with cardiac disease, twenty-two (56.4%) with hypertension and nineteen (48.7%) with cerebrovascular disease. 17.9% and 15.8% of patients presented with peripheral vascular disease and constitutional symptoms, respectively. Gastrointestinal, respiratory, and dermatological manifestations were only present in 5.1% of patients.

Table 4 depicts vessel involvement in this study:

Vertebral artery stenosis 34.6% (n=9); Common carotid artery stenosis 64.7% (n=22); Brachiocephalic artery stenosis 37% (n= 10); Subclavian artery stenosis 52.9% (n=18); Aorta arch stenosis 28.1% (n=9); Ascending aorta stenosis as well as aneurysm were equally seen 19.4% (n=6); pulmonary arteries were not involved in 72% (n=18) of cases; Thoracic aorta stenosis 38.2% (n= 13); Abdominal aorta stenosis 55.3% (n=21); Renal artery stenosis 47.4% (n=18); Mesenteric artery stenosis 29.4% (n=10); Iliac artery stenosis 18.8% (n=6).

Abdominal aorta involvement was the most frequent (71.8%, 28/39), followed by common carotid lesions (58.9%, 23/39), subclavian artery lesions (56.4% , 22/39), thoracic aorta lesions (48.7%, 19/39), renal artery lesions (46.1%, 18/39), aorta arch lesions (35.8%, 14/39), ascending aorta lesions (30.7%, 12/39), mesenteric artery lesions (28.2%, 11/39), brachiocephalic artery lesions (25.6%, 10/39), vertebral artery lesions (23%, 9/39), iliac artery lesions (17.9%, 7/39) and pulmonary artery involvement (15.3%, 6/39).

94.7% of patients were treated with glucocorticoids (n=36). 68.4% (n=26) were combined with Methotrexate and 23.7% (n=9) Azathioprine. 31,6%(n=12) were treated with Cyclophosphamide. 2.6% (n=1) was treated with Mycophenolate Mofetil (MMF). No patient was treated with Leflunomide, Cyclosporine, Rituximab, or other biologics.

Equal percentage of patients, 37.5% (n=12) showed improvement on therapy or remained stable on treatment. Twenty-five percent (n=8) had disease progression.

Complications seen were stroke in 35.5% (n=11), cardiac failure in 41.9% (n=13), renal failure in 19.4% (n=6) and 22.6% (n=7) had other complications related to medical and surgical treatment. Other complications were graft occlusion following open surgery; blindness; opportunistic infections secondary to immunosuppressive therapy and seizures complicating posterior reversible leukoencephalopathy syndrome secondary to severe uncontrolled hypertension. No patients suffered aneurysm rupture nor myocardial infarction. 71.4% (n=25) of study participants had no surgical intervention. 28.6% (n=10) had surgical management. Nine of these surgeries were open surgical procedures and one was an endovascular procedure. Surgeries included: Mechanical aorta valve replacement with aorta root repair; nephrectomy for non-functioning kidney; aorta-iliac artery bypass; bilateral carotid artery-aorta bypass; bioprosthetic aorta valve; subclavian artery bypass; femoral popliteal artery bypass and forefoot amputation.

The only endovascular intervention performed in this study was percutaneous stenting of a stenosed renal artery. It was unclear whether the four other patients had surgery as no data could be found.

Complications post-surgical intervention found were one patient suffered in-stent stenosis likely secondary to vessel wall fibrosis causing external compression. No patient suffered any neurological sequelae including TIA or stroke.

For the included study period, 75.7% (n=28) were alive on follow-up, one patient had demised and eight (21.6%) were lost to follow-up.

Table 1

Presenting feature	**Frequency (n=39)**	**Percentage (%)**
Cerebrovascular	19	48.7
Hypertension	22	56.4
Cardiac	24	61.5
Constitutional	6	15.8
Peripheral vascular	7	17.9
Gastrointestinal	2	5.1
Dermatological	2	5.1
Respiratory system	2	5.1
Other	1	2.6

Table 2

CNS feature	**Frequency**	**Percentage (%)**

Cerebrovascular accident	12	63.2
Visual disturbance	6	31.6
Transient ischaemic attack	4	21.1
Carotynia	1	5.3

Table 3

Cardiac feature		**Frequency**	**Percentage (%)**
Heart failure		18	69.2
Angina		10	37
Other		9	36
Aorta incompetence		6	24
Aorta stenosis		4	16

Table 4

Anatomical classification Based on radiography	**Aneurysm / Stenosis / Both /None**	**Frequency**	**Percentage (%)**
Vertebral artery	Aneurysm	1	3.8
	Stenosis	9	34.6
	None	16	61.5
Common carotid artery	Aneurysm	1	2.9
	Stenosis	22	64.7
	Both	1	2.9
	None	10	29.4
Brachiocephalic artery	Aneurysm	1	3.7
	Stenosis	10	37
	None	16	59.3
Subclavian artery	Aneurysm	3	8.8
	Stenosis	18	52.9
	Both	2	5.9
	None	11	32.4
Aorta arch	Aneurysm	5	15.6
	Stenosis	9	28.1
	Both	1	3.1
	None	17	53.1
Ascending aorta	Aneurysm	6	19.4
	Stenosis	6	19.4
	Both	1	3.2
	None	18	58.1
Pulmonary artery	Aneurysm	4	16
	Stenosis	3	12
	None	18	72

Thoracic aorta	Aneurysm	2	5.9
	Stenosis	13	38.2
	Both	5	14.7
	None	14	41.2
Abdominal aorta	Aneurysm	3	7.9
	Stenosis	21	55.3
	Both	5	13.2
	None	9	23.7
Renal artery	Stenosis	18	47.4
	Both	1	2.6
	None	19	50
Mesenteric artery	Aneurysm	1	2.9
	Stenosis	10	29.4
	Both	1	2.9
	None	22	64.7
Iliac artery	Aneurysm	1	3.1
	Stenosis	6	18.8
	Both	1	3.1
	None	23	71.9

Discussion

Demographic data

This study comprised of thirty-nine patients who had presented to Universitas Academic Hospital over a 21-year period from 2000 until 2021. Takayasu arteritis has a worldwide distribution, although its prevalence is higher in young females of Asian ethnicity (2)(3)(4). As Espinoza *et al*. and Danda *et al*. postulates, this higher incidence in Asian populations is due to higher frequency of HLA-B*52 expression in these populations(1)(2).

There were no patients of Asian ethnicity found in this study. Instead, the majority were of Black African or coloured ethnicity. This most likely reflects the ethnic distribution of the South African population and the specific majority ethnicity of patients seen at Universitas Academic Hospital. This is comparable to findings in South Africa by Kaawan *et al.*in their study at Tygerberg Academic Hospital in the Western Cape province(5). They found that 68% of participants were coloured and twenty-four percent were of black ethnicity. Another study done in South Africa by Mwipatayi *et al.* at Groote Schuur Hospital in the Western Cape province, looked at 272 cases over a 50-year study period. In this study 68% of participants were coloured(6). This study showed similar finding to previously documentation of sex distribution where 72% of patients were female(2)(4). The mean age at presentation was 14 years (9-23) and all patients were below 40 years of age (7). This was in line with findings from previous studies. It can also present in childhood and children usually

have differences in presentation compared to adults (1). The youngest patient included was four years of age and twelve patients were under ten years of age at the time of diagnosis.

Clinical presentation and diagnosis of Takayasu arteritis

All patients with TA fulfilled the 1990 ACR criteria for classification of TA. Not only had variability in presentation between different ethnic groups been shown, but also recent studies from Korea and Japan have shown differences between males and females (1).

Clinical heterogeneity prevails in the presentation of patients with this disease(2). This is due to the disease manifestations dependent on the pattern of arterial involvement. The disease classically presents triphasic, with the initial, pre-stenotic phase consisting of vague and non-specific systemic signs and symptoms, the active phase which leads to symptoms relating to arterial occlusion and stenosis and lastly the fibrotic, burnt-out, stenotic phase. Quinn *et al.* found in their study of 275 patients prospectively recruited from the National Institutes of Health (NIH) and Vasculitis Clinical Research Consortium (VCRC), where patients were divided into five clinical categories based on presenting feature at diagnosis, that patients do not necessarily progress through the triphasic phases of the disease(8).

Patients can present with non-specific symptoms reflecting the inflammatory nature of TA complaining of systemic symptoms including fever, myalgias, weight loss and arthralgias. In this study, 15.8% (n=6), had constitutional symptoms as presenting feature. A study by Khan *et al.*, where eighteen patients were studied, found that twenty-two percent had constitutional symptoms at disease onset (9). Danda *et al.* compared clinical features from various cohorts from around the world (2). In this study, the majority of patients presented with cardiovascular system involvement. This was documented to occur in 61.5%. In descending order of frequency: Congestive cardiac failure (69.2%, n=18); angina (37%, n=10); other cardiac involvement (36%, n=9); aorta regurgitation (24%, n=6); aorta stenosis (16%, n=4). Dilated cardiomyopathy was present in the "other" category. The aetiology of the cardiomyopathy was not elucidated, it is reasonable to assume the cause to have been ischaemic or secondary to severe prolonged hypertension. Hypertension is seen in 75% to 80% of cases of TA(10). The pathogenesis of hypertension in TA is multifactorial and complex. Hypertension is usually secondary and most frequently observed due to renal artery stenosis, followed by stenosis of the descending thoracic aorta, abdominal aorta stenosis or severe aorta regurgitation. In the present study, hypertension was seen in 56.4% (n=22) of patients. In comparison, Misra *et al*., who compared the presentation and prognosis of TA with or without ischaemic stroke or transient ischaemic attack (TIA), in a large cohort study in India reported hypertension in 73.5% of patients with stroke or TIA, and present in 81,5% of patients without stroke or TIA(11). No patient in this study had a documented myocardial infarction. Patients in this study with angina did not undergo conventional coronary artery angiography nor CT coronary angiography. The reason likely was that the study patients were not diagnosed with myocardial infarction thus requiring coronary artery angiography. As Huo *et al.* found in their study of 1580 patients with TA, between 2002 and 2021, 5.9% of patients had coexisting myocardial ischaemia and neurological symptoms (12). Neurological involvement comprised of stroke (63.2%, n= 12), visual disturbance (31.6%, n=6), TIA (21.1%, n= 4) and carotidynia (5.3%, n=1). Compared to cohorts from different countries, stroke had higher incidence in this current study. The reason for the discrepancy could be due to a smaller sample size leading to sampling heterogeneity. The risk of stroke is increased

in TA and there is also higher risk of recurrent stroke in the event of a previous stroke or TIA(11). A study from the United Kingdom, comparing primary care databases, comparing 142 patients with TA with 1371 age- and sex-matched controls, found that 13.4 % of the TA patients had stroke versus 4.9% in the control group (hazard ratio 4.38, 95% confidence interval, 2.24-8.55)(10). Haemorrhagic as well as ischaemic stroke can occur in TA. Haemorrhagic stroke usually occurs as consequence of severely uncontrolled hypertension. In the present study, only ischaemic stroke was seen. Stroke and TIA in TA can occur due to involvement of intracranial or extracranial vessels as well as, a consequence of vascular surgery procedures. In this study, patients presented with or developed stroke or TIA during follow-up and not as a consequence of vascular surgery. No patient in this study had recurrent strokes or TIA's.

Diagnosing TA can be challenging due to non-specific symptoms often predominating early in the course of the disease. It is therefore imperative that clinicians have a high index of suspicion when patients present with possible large vessel vasculitis. Diagnosis of TA is made with clinical findings and supported by imaging studies and laboratory data. In 1990, the American College of Rheumatology (ACR) developed classification criteria for TA based on the presence of six clinical criteria with the diagnosis made when three out of six criteria were met, with a sensitivity of 90.5% and specificity of 97.8%(13). These criteria were used as inclusion criteria for patients in this study.

In 2022, new classification criteria were developed and validated for use in research by the ACR/EULAR (14). These criteria are intended to use in classification of vasculitis and not to be used to diagnose vasculitis. This classification criteria aims to distinguish TA from TA mimics. These criteria include ten clinical features, a score of five or more is required to diagnose TA. Critique for the 1990 ACR classification criteria of TA was that these criteria were developed using 63 patients with TA, exclusively from North America, excluding patients from Asia as well as Europe, compared to 744 healthy controls. Pattern of arterial disease differs in these populations(14). An update on these criteria were necessary to include a wider geographical demographic and a larger patient population. The new criteria have a sensitivity of 93.8% and specificity of 99.2%. Comparing the updated 2022 ACR/ EULAR classification, all 39 patients fulfilled these criteria.

Furthermore, delay in making the diagnosis of TA worsen outcomes and leads to substantial morbidity. Factors that contribute to significant morbidity in TA are congestive cardiac failure and neurological ischaemic events such as stroke and TIA (3). Possible reasons for delay in diagnosing TA could be an alternative diagnosis made initially or patients presenting late in the course of the disease.

Disease extent and activity scores were not used in this study to quantify active disease. This is since these scoring tools were not used in the Rheumatology department. Mortality in TA is related to complications such as stroke, renal failure, heart failure or aneurysm rupture. One patient had died of unknown cause.

Role of Non-Invasive Imaging

Diagnostic imaging modalities used to delineate the arterial involvement in TA are CTA, MRA, PET CT, PET MRI, and colour doppler ultrasound (CDU). Each of these imaging modalities have their respective strengths and limitations for use. The main disadvantage of CTA is the high dose of ionising radiation used as well as limitations in CTA for follow-up due to the radiation exposure and other contraindications with contrast usage(2).

Computer tomography angiography (CTA) was used in this study to evaluate vascular involvement. Magnetic resonance angiography (MRA) remains the gold standard for radiological diagnosis of TA, however, due to lack of availability of MRA, ease of access, and long waiting periods for MRA, CTA was used to diagnose TA. No patient in this study had MRA imaging performed. CTA reveals narrowing of the arterial lumen and aneurysmal lesions with vital information on the vessel wall. This includes features such as wall thickening and calcification and effect of contrast enhancement.

Response to therapy is monitored with repeat angiographic imaging, initially six to twelve monthly during the first two years on treatment and thereafter yearly. In Tombetti and Mason's prospective study, patients on treatment were followed up with MRA for a median of eighteen months. They concluded that 40% of arterial lesions remained stable, 37% showed disease progression and twenty-three percent showed improvement on treatment. Based on the response, assessed clinically, with laboratory parameters of inflammation and with imaging, GCs can be tapered to ≤ 5mg per day, with careful and systematic patient monitoring for relapse. Relapse is common after tapering or stopping IS therapy. Comarmond *et al.* concluded in their French study, including 318 patients, over a 44-year study period, that 50% of patients will suffer relapse and suffer a vascular complication within ten years of diagnosis(15).

Angiographic findings

Abdominal aorta involvement was the most frequent (71.8%, 28/39), followed by common carotid lesions (58.9%, 23/39), subclavian artery lesions (56.4%, 22/39) and thoracic aorta lesions (48.7%, 19/39).

Therefore, Numano type IV was most commonly found in this study followed by Numano type I and type IIa. Type III was the least common. Cluster one was therefore the most abundant in this study.

Recently, Goel *et al.*'s cluster analysis strategy, classified patients into three distinct subsets using the pattern of arterial involvement. Patients in cluster one have more vascular disease in the abdominal aorta, renal and mesenteric arteries. Patients in cluster two have bilateral disease in the carotid and subclavian arteries and cluster three patients usually have asymmetrical disease in fewer vascular territories(16).

Treatment

Immunosuppression (IS) has remained the cornerstone of treatment for TA. TA requires long term immunosuppressive therapy and has a high relapse rate on tapering or stopping of IS. Clinical remission is the ultimate goal of therapy, but this is not always achieved in patients

with TA. Induction is usually achieved with high dose glucocorticoids (GC), 1mg/kg/day, combined with conventional disease-modifying anti-rheumatic drugs (cDMARDs). The most frequently used combination was GC with Methotrexate (MTX), followed by Azathioprine (AZA). Cyclophosphamide (CYC) was used only in paediatric patients included in this study. CYC is usually reserved for patients who present with severe, life-threatening disease or relapse on conventional IS therapy. Biological therapies have emerged as promising treatment strategies where patients relapse on cDMARDs or show progressive disease despite adequate immunosuppression. Biological therapy was not used on any patients in this study.

Surgery in TA can be considered when medical therapy has failed or when the disease remains refractory with severe end-organ ischaemia. A recent study in 2020 by Porter *et al*. concluded that patients with symptomatic cerebrovascular disease from severe supra-aortic stenosis, improved with biological therapy and did not require surgical intervention(17). Indication for surgical intervention in TA are critical arterial stenosis with end organ damage, aneurysm rupture, severe aortic regurgitation due to aneurysmal dilatation of the aorta root. In-stent stenosis is an important complication post-surgery(18). External stent compression by progressive vessel wall fibrosis and calcification was suggested to contribute to this complication.

The association between chronic inflammatory diseases and increased incidence of cardiovascular disease and accelerated atherosclerosis has clearly been established, therefore it is of vital importance that cardiovascular risk management be addressed(3).

Study Limitations

The following study limitations are to be considered and include, small sample size, single center experience and non- standardisation in obtaining clinical and radio-graphical data. This was due to clinical data not comprehensively recorded by colleagues and differences in reporting of radiology reports. Suggested corrections by the examiner are acknowledged and were discussed with research supervisor. These include duration of treatment with immunosuppressant drugs and method of measurement of improvement.

Recommendation for future studies

Future studies can be done to focus on ways in identifying patients with Takayasu arteritis earlier and exploring to identify novel biomarkers for use in diagnosis and disease activity assessment. Progress in the management of this challenging disease will depend on the future study of patients treated with biologics earlier in the course of the disease and comparing their outcome with patients on conventional disease modifying agents.

Conclusion

Takayasu arteritis remains a rare albeit relevant disease of young females leading to significant morbidity and mortality if the diagnosis is delayed. The diagnosis of TA is often missed due to low clinical awareness and variable clinical presentation. Diagnosing TA remains challenging. Thus far, no biological marker specific to TA has been identified. No standardised criteria exist to assess disease activity, further contributing to the difficulty in managing the disease. Imaging is paramount to making the diagnosis, establishing the extent

of arterial involvement, and assessing disease progression and response to treatment. Immunosuppression with combination cDMARDs remains the mainstay of treatment. Surgery is indicated in certain clinical scenarios. Early and timely access to biologics in refractory or relapsing disease can negate the need for surgical intervention and might have an effect on morbidity and mortality. This study provides a valuable contribution to the body of knowledge about TA in the South African setting with the first study done on patients from the Free State province.

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Appendix A

Health Sciences Research Ethics Committee

29-Jul-2022

Dear **Dr Eugenie Botha**

Ethics Clearance: **An Overview of Takayasu Arteritis at an Academic Hospital in Central South Africa**

Principal Investigator: **Dr Eugenie Botha**

Department: **Internal Medicine Department (Bloemfontein Campus)**

Submission Page

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2022/0116/2908**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

Research conducted in any Department of Health facility: Researchers are required to sign and return the HSREC approval letters to the provincial Department of Health where they applied. It is also a requirement for researchers to submit electronic copies of their final research findings, and/or make a presentation of their findings and recommendations at departmental research days when and where indicated.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2020); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; International Council for Harmonisation (ICH) Harmonised Guideline, Integrated Addendum to ICH E6(R1), Guideline for Good Clinical Practice (GCP) E6(R2), 2016, SAHPRA Guidelines as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Prof. A. Sherriff
Chairperson: Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
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Appendix B

health
Department of Health
FREE STATE PROVINCE

18 July 2022

Dr Eugenie Botha
Internal Medicine Department
University of Free State

Dear Dr E Botha

Subject: An Overview of Takayasu Arteritis at an Academic Hospital in Central South Africa

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Participation in the study must be voluntary
- A written consent by each participant must be obtained.
- Serious adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day-to-day running of **Universitas Hospital** nor the performance of duties by the respondents or health care workers.
- The DOH expects that the researcher will be the responsible data manager according to the POPI Act. The responsibility thus lies with the researcher to ensure that the processing of all participant's personal information and research data is lawful according to the stipulations of the POPI Act (Protection of Personal Information Act 4 of 2013).
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- Department of Health to be fully indemnified from any contravention of the POPI Act as you conduct this study.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sebeelats@fshealth.gov.za/gwantshuws@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with Institution Manager on commencement for logistical arrangements.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- **As part of feedback you will be required to present your study findings/results at the Free State Provincial health research day**

Trust you find the above in order.

Kind Regards

MR. MNG MAHLATSI
HEAD: HEALTH

Date: 21/07/2022

Head: Health
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Appendix C

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA
UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

31 January 2022

For attention: Ethics Committee

Faculty of Health Sciences

Title of project:

An Overview of Takayasu Arteritis at an Academic Hospital in Central South Africa.

Researcher:

Dr Eugenie Botha

I have given input regarding the above-mentioned project's protocol on the following aspects of the protocol, namely the study design, sample, measurement, and statistical analysis.

The input will be implemented under the supervision of the study leader.

Yours faithfully,

Dr Joseph B Sempa

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Appendix D

An Overview of Takayasu Arteritis at an Academic Hospital in Central South Africa

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Introduction

Vasculitides are a heterogeneous group of systemic inflammatory diseases, characterised by inflammation and damage to blood vessels. The consequence may be ischemia and damage to the tissues or organ supplied by the affected blood vessels.

Any type, size or site of blood vessel may be involved. Vasculitis can be primary/idiopathic or secondary due to another underlying disease. While the inflammation can be confined to a single organ, it may also involve multiple organ systems. Classification is based on the size of the affected vessel and is classified as small-vessel, medium-vessel and large-vessel vasculitis.

Background and History

Earliest published data about TA dates back as far as 1830. Mikito Takayasu, Professor of Ophthalmology at Kanazawa University, Japan, presented the case of a woman with characteristic abnormal fundal arteriovenous findings in 1908 (1). It was Takayasu's colleagues, Katsutomo Ohishi, and Tsurukichi Kagoshima, however, who in a later academic discussion, described the more typical cases of patients with absent pulses (1)(2)(3).

In 1939, several cases were reported in Japan, when Yasuzo Shinmi, used the term 'Takayasu's Arteritis' for the first time. TA has been well known in many countries outside of Asia, since Kentaro Shimizu and Keiji Sano, surgeons at Tokyo University, introduced this disease in the English literature as pulseless disease in 1951. Furthermore, in 1952, a paper on TA by Caccamize and Whiteman in the American Heart Journal led to the distribution of information on TA into Western countries (4).

Ross and McKusick summarized over 100 cases in which absent or diminished pulses in the arms and neck were found, and they dubbed the term 'aortic arch syndrome'. They recognised the cases according to the cause of disease as either syphilitic, congenital abnormality, atherosclerotic or traumatic. They cited four cases in their case series as 'young female arteritis', noting these patients as having characteristic ocular and cerebral vascular findings (4).

In 1963, Hideo Ueda, Professor of Internal Medicine at Tokyo University, studied cases of TA and confirmed pan aortitis involving the aorta and its main branches and referred to it as 'pan aortitis syndrome'. Professor Ueda suggested an autoimmune aetiology and later renamed it 'aortitis syndrome' to avoid confusion of involvement of the whole aorta (4). In 1975, in honour and recognition of Takayasu as first reporting the disease entity, the research committee of the Department of Health and Welfare in Japan, suggested 'Takayasu Arteritis' (4).

Literature review

Available literature on TA focuses on describing the clinical features and management of the disease. These prior studies highlight that TA is still of unknown aetiology with often late and advanced presentation. Most of the data originates from Asia with sparse data available on a sub-Saharan /population and specifically South Africa (5). No data are available about TA in the Free State.

Multiple authors have attempted to correlate the pattern of disease involvement to their population demographic (2)(5)(6). Variation in pattern of disease has been demonstrated in some studies, with comparative study showing Japanese patients having disease more frequently of the aorta arch and its branches than Korean and Indian patients who had disease of the abdominal aorta (7).

TB has been postulated as a possible aetiology, which is of particular interest in the South African context, keeping in mind the high burden of disease in South Africa (8)(9). It is difficult to establish a causal relationship between TB and TA. With high prevalence of TB in South Africa, the implication may be an incidence higher to other countries where TB is not endemic, which has not been established.

Definition

Takayasu arteritis (TA) is a chronic granulomatous inflammatory vasculitis of large and medium vessels of unknown aetiology (10) (11). It has a predilection for the aorta and its branches, such as

the brachiocephalic, carotid, subclavian, vertebral and renal arteries, as well as the coronary and pulmonary arteries. Expression of the disease is variable, often leading to ischemic symptoms due to blood vessel stenosis or thrombus formation. Disease progression causes tunica media destruction, often with resultant aneurismal formation or acute aneurismal dissection of affected arteries.

Characterised histologically as 'panarteritis', resulting in intimal thickening, destruction of medial smooth muscles and elastic layers, cellular infiltration in the media with cellular infiltration around the vasa vasorum.

Epidemiology

TA has a worldwide distribution with the highest prevalence in the Asian population. The disease is more common in young females with a male to female ratio of 1:4-9. The incidence in Asian countries is reported as 1 to 2 cases/million per year and an estimated prevalence of 12.9 to 40 cases/million (3).

TA may show different patterns of arterial involvement, disease expression and prognosis in different regions of the world (12) (13). In contrast to Asia, the incidence has been reported as 0.3 cases/million in the United Kingdom (14). Recent epidemiologic studies suggested that TA is being increasingly recognised in Europe with a reported incidence rate between 0.4 to 1.5 per million (15).

Available data on the African continent and specifically South Africa is limited. The largest study on adults with TA in SA was done in the Western Cape Province at Groote Schuur Hospital. This was a retrospective, descriptive study spanning over 50 years and included 272 patients (16).

Case reports have been documented in South Africa and Africa (17). Published literature in South Africa mainly has been focused on TA in the paediatric population group, and, in the Free State Province of South Africa, no published literature has been found.

Clinical presentation

Clinical manifestations are variable, ranging from initially asymptomatic to vague and non-specific symptoms, to limb claudication, systemic and renovascular hypertension to cerebrovascular accidents.

Non-specific symptoms include fever, malaise, weight loss, myalgia or arthralgia. As the disease progresses, classical features of TA begin to emerge with ischemic symptoms being a prominent feature. Hypertension due to stenosis of the aorta or renal artery is a common presentation.

The following are disease features:

- Constitutional symptoms: fever, weight loss and fatigue – common in early phase of the disease
- Arthralgia/Myalgia: intermittent or continuous and chronic in nature
- Carotidynia: tenderness on palpation of a carotid artery in 10 to 30 percent of patients
- Absent or weak peripheral pulse(s): most common at radial arteries and is often asymmetric

unusual cases of acute vessel occlusion occur with limb gangrene or ischemic ulcerations; however, this is uncommon due to the formation of collateral circulation indicating the chronic nature of disease development

• Claudication: limb claudication is a common presenting symptom. Subclavian steal syndrome can lead to neurological symptoms or syncope related to exercise induced redirection of blood flow to the upper limb. This results from a stenotic lesion proximal to the origin of the vertebral artery. Other symptoms of claudication include mild to severe upper- or lower limb pain with activity often causing functional impairment

• Arterial bruit: in patients with stenotic lesions, bruits are audible over the stenosed vessels. Signs and symptoms of aortic stenosis or aortic incompetence can also be present

• Blood pressure discrepancy between the arms (anisosphygmia)

• Hypertension: due to coartation of the aorta or renal artery stenosis

• Angina pectoris: myocardial ischemia can occur due to narrowing of coronary artery ostia from aortitis or coronary arteritis. This can lead to myocardial infarction and death

• Mesenteric artery ischemia with involvement of abdominal aorta causing post-prandial pain, diarrhoea, and gastrointestinal haemorrhage

• Skin lesions resembling pyoderma gangrenosum or erythema nodosum

• Neurological involvement: involvement of the vertebral and carotid arteries with sequelae of decreased cerebral blood flow- dizziness, syncope, orthostasis and stroke. A late manifestation of severe disease is visual impairment

• Respiratory manifestations include dyspnoea, chest pain, haemoptysis, and pulmonary hypertension. Heart failure can be the presenting symptom due to aortic incompetence, systemic hypertension, or myocarditis.

Diagnosis

The classification of TA requires at least three of the six criteria of the American College of Rheumatology of 1990 to be present. The ACR criteria for TA consist of:

1. Age of onset before 40 years old.

2. Claudication of an extremity.

3. Decreased brachial artery pulse.

4. A difference of more than 10 mmHg systolic pressure between two limbs.

5. A bruit or the subclavian arteries or the aorta.

6. Angiographic evidence of narrowing or occlusion of the aorta, its primary branches, or large arteries in the proximal upper or lower extremities.

• The presence of 3 or more out of 6 of this criteria has a sensitivity of 90.5% and a specificity of 97.8 % (10).

• There is often a delay in the diagnosis due to non-specific symptoms and variable clinical presentation (19).

• The diagnosis is often missed due to low clinical awareness and suspicion (5). No standardized criteria to assess disease activity have been formalized, further contributing to the difficulty in managing the disease. Thus far, no established biological marker specific to the diagnosis of TA has been identified (5). Imaging is paramount to making the diagnosis, establishing the extent of arterial involvement, and assessing disease progression and response to treatment (20).

• There is poor correlation between systemic markers of inflammation and inflammation in the vessel wall. Therefore, TA may be active without increasing CRP or ESR, and vice versa. In patients with apparent clinical and laboratory remission, arterial specimens may show histological signs of vasculitis. Imaging allows to distinguish between different types of TA, depending on the location of vascular lesions (5).

• The diagnosis is infrequently made histologically since biopsy of large vessels is impractical (12). However, the diagnosis can be made when an arterial biopsy is available after a revascularizing procedure or repair of an aneurysm.

Imaging modalities used for diagnosis and follow-up:

Magnetic resonance angiography (MRA) or computerized tomography angiography (CTA) is used to establish the diagnosis of TA. CTA is most often used in our setting due to restrictions to the accessibility of MRI. MRA and CTA are helpful for the evaluation of the aorta and its primary branches. CTA may provide excellent anatomical characterization of structural changes in the aorta but may not detect early disease activity. Although MRA can show vessel wall thickening, oedema, and contrast enhancement, it has been shown that correlation with clinical activity or systemic inflammation is poor and it is shown to have a limited role for long-term follow-up (13).

Conversely, Colour Doppler Ultrasonography (CDU) is helpful in evaluating the temporal, carotid, axillary, and femoral arteries, but it fails to depict the thoracic aorta unless performed as a transoesophageal examination. Similar to MRA and CTA, CDU can not only visualize luminal changes, stenoses, and aneurysms of large arteries; it can also detect the characteristic homogeneously thickened vessel walls, as well as mural inflammation and oedema, which are early inflammatory signs. CDU also provides better resolution than MRA and CTA. There is no risk of radiation exposure in MRA and CDU. Disadvantages of MRA include overestimation of vascular occlusions and inability to visualize small branch vessels and vascular calcifications (13).

Positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG PET) is a non-invasive imaging method that measures 18F-FDG, which accumulates in hyper metabolic, activated inflammatory cells infiltrating the vessels. 18F-FDG PET/CT combines the functional information from PET and the anatomical information from CT. 18-FDG-PET is the most sensitive test for early vessel inflammation (13). Therefore, both early vascular inflammation and its location in the aorta and its branches may be detected using PET-CT in the first two phases, which may help in the early diagnosis of TA. However, vascular uptake on PET is not specific for vasculitis, and discriminating between atherosclerotic and vasculitic lesions may be challenging. Unfortunately, PET cannot delineate the vessel wall structure and luminal flow; another disadvantage is high radiation exposure with PET-CT imaging (13).

The Numano classification classifies the disease into 5 types based on radiographic involvement:

Type 1: Branches from aortic arch

Type 2a: Ascending aorta, aorta arch and its branches

Type 2b: Ascending aorta, aortic arch, its branches and descending thoracic aorta

Type 3: Thoracic descending aorta, abdominal aorta and or renal arteries

Type 4: Abdominal aorta and or renal arteries

Type 5: Combined features of 3 and 5.

Differential diagnosis includes:

- Infections (tuberculosis, syphilis, Staphylococcus aureus, Salmonella, cytomegalovirus, herpes virus, hepatitis viruses and HIV)
- Malignancies (e.g., leukaemia, lymphoma, glioma)
- Immunodeficiency disorders
- Paraneoplastic syndrome
- Post radiation therapy
- Autoimmune secondary vasculitis (systemic lupus erythematosus, spondyloarthritis, sarcoidosis)
- Renal disorders
- Drugs (cocaine, sympathomimetics)
- Livedoid vasculopathy
- IgG4- related disease
- Fibro -muscular dysplasia
- In children TA should not be overlooked when suspecting inherited disorders (e.g., Marfan's syndrome, Ehlers Danlos' syndrome type IV, neurofibromatosis type I, fibro muscular dysplasia, Grange syndrome).
- Other primary vasculitides (Behçet's disease, Kawasaki's disease and Buerger's disease). In contrast, in adult patients, TA should not be overlooked in cases of atherosclerosis and arteriolosclerosis (hypercoagulable states – thrombotic thrombocytopenic purpura, antiphospholipid syndrome), vasospastic disorders (such as reversible cerebral vasoconstriction syndrome, posterior reversible encephalopathy syndrome)
- Vasculitis mimic

Pathogenesis

The exact aetiology of TA is unknown. The pathology is characterised by the involvement of all arterial layers. Activation of vasa vasorum endothelial cells and recruitment of lymphocytes is involved in the pathological process of TA (35).

The vasa vasorum is considered a portal entry of inflammatory cells and the cellular infiltrate is comprised of CD4+ T cells, CD8+ T cells, γδT cells, natural killer (NK) cells, macrophages, and neutrophils (11) (21). TNF-α production occurs primarily in macrophages, T- cells and NK cells. TNF-α is important in the formation of granuloma (22) (23). Pathological findings based on aortic tissues

samples showed that γδT and NK cells are engaged with apoptosis of endothelial cells by production of perforin and killer cell lectin-like receptor subfamily K (NKG2D) (24).

The γδT and NK cells expressing NKG2D receptors recognize MICA (the major histocompatibility class I chain-related A) on vascular smooth muscle cells and release perforin and other mediators, leading to acute inflammation. Pro-inflammatory cytokines are also released from the natural killer and Tcells, inducing the production of matrix metalloproteinase (MMPs) and amplifying the inflammatory response. This leads to an increase in the major histocompatibility complex (MHC) antigen and recruitment of more mononuclear cells within the vascular wall. Histocompatibility complexes are activated through Toll-like receptors. Peripheral T-cells in patients with TA were reported to be in an active state with increased CD4/CD8 ratio, suggesting dominant role of T-helper cells (25).

Th1 lymphocytes, through the production of interferon-γ, lead to the formation of giant cells through activation of macrophages which release of vascular endothelial growth factor (VEGF). VEGF causes increase in neovascularisation and release of platelet-derived growth factor (PDGF). This ultimately results in smooth muscle migration and intimal proliferation. Th17 cells induced by the IL-23 microenvironment also contribute to vascular lesions through activation of infiltrating neutrophils (26). B-cell contribution of TA remains controversial.

Anti-epithelial cell antibodies (AECA) and anti-aorta antibodies were reported to be found in patients with TA (27). AECAs have been detected in a wide range of pathological conditions, including systemic vasculitis. There is much evidence that AECAs play pathogenic roles in vasculitis, in endothelial cell activation and induction of apoptosis (28). There are also reports that TA patients often have antiphospholipid antibodies especially anti-cardiolipin, anti-annexin V and anti-β2 glycoprotein-I antibodies (29). It remains unclear whether these antibodies have a pathogenic role in TA.

TA patients' sera have been shown to contain other antibodies such as anti-human heat shock protein60/65 auto antibodies (30). However, none of them have proven specificity to TA. Patients with TA have been shown to have elevated IL-6, IL-8, IL-16 and IL-18 levels, with IL-16 and -18 correlating well with disease activity (31). The association of TA with HLA alleles suggests that genetic factors are involved in the pathogenesis of TA.

These genetic factors, both within and outside the HLA region, were examined and it was concluded that HLA-B*52 is the only gene that shows an association with TA beyond ethnicity (32).

A recent large scale genetic association study that involved Turkish and North American-European patients has identified and confirmed two independent susceptibility loci within the HLA region HLAB/MICA and HLA-DQB1/HLA-DRB1. This study revealed an association between TA and HLA-B*52 also in North American-European patients (33). Recent studies have shown that TA has been associated with various non-HLA susceptibility loci (15).

Treatment

Treatment for TA can be subdivided into medical and surgical treatment. The goal of treatment is to suppress vascular inflammation. In cases with critical arterial stenosis or marked aneurysmal formation, endovascular and/or open surgical procedures can be considered. As a rule, surgical interventions should follow suppression of vascular inflammation by the appropriate

immunosuppressive therapy (34). Therefore, to optimally treat TA, the degree of disease activity as well as the pattern and extent of arterial involvement should be known.

Active disease is defined by the **EULAR consensus** definition as:

1) The presence of typical signs or symptoms of active LVV (large vessel vasculitis).

2) At least one of the following

a. Current activity on imaging or biopsy.

b. Ischaemic complications attributed to LVV

c. Persistently elevated inflammatory markers (after other causes have been excluded (35).

Medical treatment

Corticosteroids form the cornerstone of initial immunosuppressive (IS) therapy. Conventional second line treatment consists of Methotrexate, Mycophenolate mofetil, Leflunomide and Azathioprine, alone or in combination with GC to facilitate tapering of the GC dose.

Cyclophosphamide is also an option but is usually reserved for severe or refractory cases, due to the well-known long term adverse effects such as gonadal suppression.

Although there are no widely accepted criteria for definition of refractory disease, the Turkish Takayasu Arteritis Study Group has issued a definition and is used (36):

1. Clinical or angiographic progression despite treatment

2. The presence of any of the following characteristics:

• Prednisone dose >7.5 mg/day after 6 months of treatment, despite administration of conventional IS agents.

• New surgery due to persistent disease activity.

• Frequent attacks (more than three per year).

• Death associated with disease activity; and

• In cases of refractory disease, biological agents such as Rituximab (RTX), Tocilizumab (TCZ), TNF inhibitors (TNFi) and Abatacept (ABA) can be used. Biological agents are increasingly used. Observational studies provide evidence that biological agents such as Tocilizumab and anti-tumor necrosis factor are beneficial and could be used effectively in refractory TA (37).

Surgical treatment

In the late presentation and chronic phases of TA, where vascular lesions are irreversible with medical treatment alone, surgery or endovascular interventions may be considered.

In cases of severe ischemic symptoms of an extremity or severe ischemia to an organ, revascularisation by either endovascular or surgical intervention may be necessary.

Important indications for surgery are symptomatic cerebral artery stenosis causing cerebrovascular ischemia; coronary artery ischemia; abdominal aorta aneurysm and aortic bifurcation disease with lower limb claudication and ischemia; hypertension caused by renal artery stenosis; severe aortic regurgitation and severe stenosis of the aorta arch (38)(39)(40)(41).

Pregnancy and Fertility

Pregnancy is generally not associated with disease progression; nevertheless, pregnant patients with TA should be managed in a high-risk obstetric unit. Complications posing maternal risk are attributable to systemic hypertension leading to the development of pre-eclampsia, exacerbation of chronic hypertension, heart failure and cerebral vascular accidents. Foetal complications such as growth restriction are as a result of impaired placental blood flow secondary to uncontrolled hypertension and involvement of the abdominal aorta. Another reason for growth restriction is stenosis of the renal arteries with increased production of renin, causing increased blood pressure (42). Fertility is not directly affected by TA; however, counselling about the risks of teratogenicity of certain immunosuppressive drugs is necessary (42).

Complications and Prognosis

The natural history and prognosis of TA remains poorly defined. This is due to lacking data for long term follow up. Prognosis mainly depends on the development of complications, albeit from the disease itself or as a consequence of medical or surgical treatment. Further important prognostic factors are duration and severity of both systemic and vascular inflammation, late presentation and diagnosis and treatment resistance (4).

Other contributors to poor prognosis include: the presence of Takayasu retinopathy, renal artery stenosis with renovascular hypertension, aortic regurgitation, aortic aneurysm, and/or co - morbidities mostly resulting from corticosteroid treatment (4). Hypertensions as well as accelerated atherosclerosis due to chronic inflammation are important complications which need early identification and treatment (43). In-stent stenosis is an important complication post-surgery (44). External stent compression by progressive vessel wall fibrosis and calcification was suggested to contribute to this complication.

Usual causes of death in patients with TA are myocardial infarction, congestive cardiac failure, renal failure, aneurysm rupture and cerebrovascular accidents (45).

Aim of the study

This single centre, retrospective study aims to provide data on Takayasu arteritis which has largely been undocumented in South Africa, with no existing data in the Free State. This study will provide a valuable contribution to the description of TA in the Free State province.

Objectives

1. Describe the clinical, radio graphical features and treatment of TA of patients at Universitas Academic Hospital in the Free State.

Methodology

2.1 Study design

This is a retrospective descriptive study, which will be done at Universitas Academic Hospital, in the city of Bloemfontein, Free State.

2.2 Study participants

Patients seen at Universitas Academic Hospital, that fulfil the American College of Rheumatology 1990 criteria for Takayasu Arteritis, will be included. The proposed study period is 2000-2021.

Patients are referred to Universitas Academic Hospital from other centrally located provinces in South Africa, including the Northern Cape and the Eastern Cape as well as the neighbouring country of Lesotho. An estimated number of 5-10 new patients are seen per year. Adult as well as paediatric patients will be included.

2.2.1 Inclusion/ exclusion criteria

2.2.1.1 Inclusion criteria

Fulfil ACR 1990 criteria for Takayasu Arteritis.

Seen at Universitas Academic Hospital Rheumatology, Vascular surgery, or Paediatric divisions.

2.2.1.2 Exclusion criteria

Missing data on clinical features or CT angiography not performed.

Uncertainty of diagnosis or disease due to secondary causes.

2.3 Data measurement

I will obtain the Department Vascular surgery weekly statistics, dating from 2017. This is the year when Dr Asha Malan joined the department. By searching the key words “Takayasu Arteritis” and “large vessel vasculitis”, I will identify patients diagnosed with TA.

I will also gather the records of vascular surgery annual surveillance admissions for known patients with TA.

Files from the vascular laboratory from the Vascular Surgery Unit will also be accessed.

I will search the Rheumatology clinic, Paediatric clinic as well as the Vascular Surgery Clinic archives from the year 2000 until 2021 to identify patients with TA.

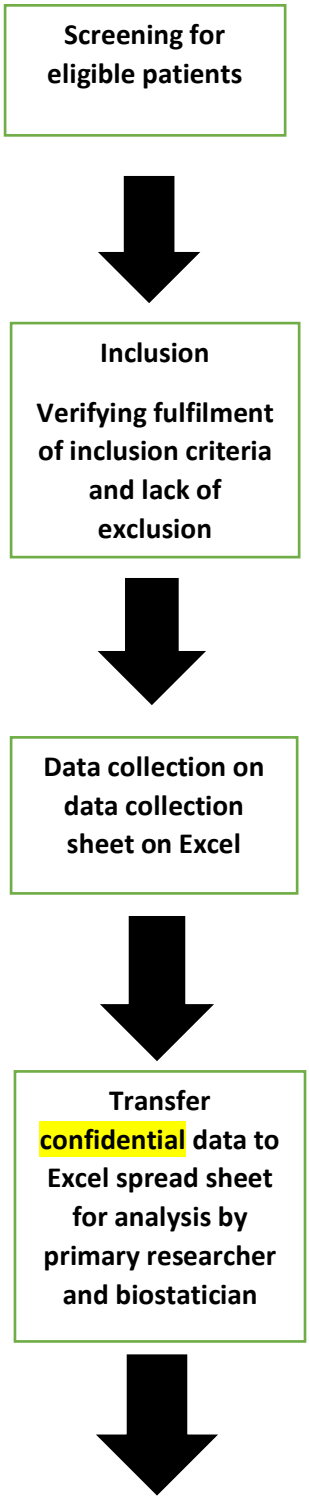
I will liase with Dr Mari Wentzel, a registrar at the Department of Radiology, Universitas Academic Hospital as an Internal Collaborator, to extract aortograms with the aim of possibly including more patients with TA.

Data to be collected will be patient demographics such as age, race, and sex, clinical- (including presentation) and radio graphical features as well as treatment received.

The scientific rationale for ethnic data collection is that the disease is mostly found in patients of a certain ethnic descent. We would like to correlate this with the South African demographic.

The disease predominantly occurs in young women with a male to female predominance of 1:4-9.

Therefore, the aim of collecting data on gender is to establish if this female predominance is correlated in the South African setting.



Data presentation and finalisation

2.4 Methodological and Measurement errors

The possible confounding factor might be in the form of incorrect patient inclusions as a result of misdiagnosis – there is significant overlap between the auto-immune vasculitides. The appropriateness of the diagnosis will also be reviewed by a rheumatologist prior to inclusion.

The measure that I plan to use in this case will be the inclusion of patients with a confirmed diagnosis using the ACR 1990 criteria for TA.

2.5 Pilot Study

After getting final approval from the Health Sciences Research and Ethics Committee (HSREC), the first five patients will be selected from the eligible patient pool, a preliminary statistical extrapolation will be compiled to assess the measurability of the proposed parameters using the proposed data collection tool (see appendix 1). The researcher will share a copy of the pilot study with the biostatistician to ensure that the data is captured appropriately.

2.6 Data Analysis

Data analysis will be done with assistance from University of Free State Department of Biostatistics. Data will be exported to excel and shared with the biostatistician for analysis. A separate password protected study participant list with study numbers (pseudo-anonymisation) will be made and this will be shared for statistical analysis. To describe the patient samples, categorical data will be summarised into frequencies and percentages, while for numerical data, we shall use means and standard deviations for normally distributed data and median and interquartile ranges for skewed data.

2.7 Ethical considerations and confidentiality

Written permission will be obtained from the Free State Department of Health (FSDoH).

The protocol will be submitted for ethics approval to the Health Sciences Research Ethics Committee (HSREC)- University of the Free State (UFS).

Patient identities will be kept confidential. Data will be kept on a password protected computer, only accessible to the principal investigator. Data sheet information will be provided to the Department of Biostatistics and transfer of data onto a spread sheet will be kept confidential.

2.8 Time Schedule

Task	Responsible Person	Planned Start Date	Planned Finish Date

Protocol Development	Primary Investigator Supervisor and Co-Supervisors	April 2021	May 2022
Presentation at Departmental Evaluation Committee	Primary Investigator	November 2021	November 2021
Submission of Protocol Draft to Biostatician	Primary Investigator	January 2022	January 2022
Await feedback and meeting with Biostatician	Primary Investigator Biostatician	January 2022	January 2022
Finalise Protocol	Primary Investigator Supervisor and Co-Supervisors	February 2022	May 2022
Submit Protocol to HSREC UFS	Primary Investigator	March 2022	March 2022
Conditional HSREC Approval	HSREC	April 2022	May 2022
Submit Request for Approval from FSDoH	Primary Investigator	May 2022	July 2022
Data Collection for Pilot Study	Primary Investigator	May 2022	June 2022
Pilot Study Data set submission for Biostatician review	Primary Investigator Biostatician	July 2022	August 2022
Data Collection and Data Audit	Primary Investigator Biostatician	September 2022	October 2022
Data Analysis	Primary Investigator Biostatician	November 2022	December 2022
Manuscript Preparation for Final Submission	Primary Investigator Supervisor and Co-Supervisors	January 2023	May 2023
Manuscript Submission	Primary Investigator	June 2023	June 2023

2.9 Budget

Printing costs	R300
Language editing	R 2000
Binding of final draft	R200

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Appendix E

Data sheet

Record ID	_____
Your study ID	_____
Sex	◯ Male ◯ Female ◯ No data
Age at presentation	_____
Ethnicity	◯ Black African ◯ White ◯ Coloured ◯ Indian ◯ Asian ◯ No data
ACR criteria	☐ Age of onset before 40-years ☐ Claudication of an extremity ☐ Decreased brachial artery pulse ☐ Difference of > 10mmHg systolic pressure between 2 limbs ☐ Bruit over subclavian artery or aorta ☐ Angiographic evidence of narrowing or occlusion of aorta/ aorta primary branches/large arteries limbs ☐ No data
Clinical features	☐ Cerebrovascular ☐ Hypertension ☐ Cardiac ☐ Constitutional symptoms ☐ Peripheral vascular ☐ Gastrointestinal symptoms ☐ Skin lesions ☐ Respiratory manifestations ☐ Other ☐ No data
Cerebrovascular	☐ Cerebrovascular accident ☐ Transient Ischemic accident ☐ Syncope ☐ Visual disturbance or fallout ☐ Carotynia ☐ No data
Cardiac features	☐ Aorta stenosis ☐ Aorta incompetence ☐ Angina ☐ Heart failure ☐ Myocardial infarction ☐ Other ☐ No data

Constitutional	☐ Fever ☐ Weight loss ☐ Malaise ☐ Arthralgia ☐ No data

Anatomical classification based on radiography

	Yes	No	No data
Vertebral artery	◯	◯	◯
Common carotid artery	◯	◯	◯
Brachiocephalic artery	◯	◯	◯
Subclavian artery	◯	◯	◯
Aorta arch	◯	◯	◯
Ascending aorta	◯	◯	◯
Pulmonary artery	◯	◯	◯
Thoracic aorta	◯	◯	◯
Abdominal aorta	◯	◯	◯
Renal artery	◯	◯	◯
Mesenteric artery	◯	◯	◯
Iliac artery	◯	◯	◯

Aneurysm or stenosis of vertebral artery	◯ Stenosis ◯ Aneurysm ◯ Both
Aneurysm or stenosis of common carotid	◯ Stenosis ◯ Aneurysm ◯ Both
Aneurysm or stenosis of brachiocephalic artery	◯ Stenosis ◯ Aneurysm ◯ Both
Aneurysm or stenosis of subclavian artery	◯ Stenosis ◯ Aneurysm ◯ Both
Aneurysm or stenosis of aortic arch	◯ Stenosis ◯ Aneurysm ◯ Both
Aneurysm or stenosis of ascending aorta	◯ Stenosis ◯ Aneurysm ◯ Both
Aneurysm or stenosis of pulmonary artery	◯ Stenosis ◯ Aneurysm ◯ Both
Aneurysm or stenosis of thoracic aorta	◯ Stenosis ◯ Aneurysm ◯ Both

Aneurysm or stenosis of abdominal aorta	◯ Stenosis ◯ Aneurysm ◯ Both
Aneurysm or stenosis of renal artery	◯ Stenosis ◯ Aneurysm ◯ Both
Aneurysm or stenosis of mesenteric artery	◯ Stenosis ◯ Aneurysm ◯ Both
Aneurysm or stenosis of iliac artery	◯ Stenosis ◯ Aneurysm ◯ Both
Surgical procedures	◯ Endovascular intervention ◯ Open surgery ◯ Surgery - not specified ◯ No surgical intervention ◯ No data
Response to therapy	◯ Improvement on therapy ◯ Stable with neither disease improvement or progression ◯ Disease progression ◯ No data
Medical treatment	☐ Glucocorticoids ☐ Methotrexate ☐ Leflunomide ☐ Azathioprine ☐ Mycophenolate mofetil ☐ Cyclosporine ☐ Rituximab ☐ Other biological agents ☐ No data
Complications of disease	◯ Stroke ◯ Cardiac failure ◯ Renal failure ◯ Renal failure ◯ Rupture of aneurysm ◯ Other ◯ No data
Outcome	◯ Lost to follow up ◯ Dead ◯ Alive ◯ No data

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Chapter 1

Executive summary

Purpose of the study Takayasu arteritis (TA) is a chronic granulomatous inflammatory vasculitis of large and medium vessels of unknown aetiology. It has a predilection for the aorta and its branches, and can affect the brachiocephalic, carotid, subclavian, vertebral, and renal arteries, as well as the coronary and pulmonary arteries. Expression of the disease is variable, often leading to symptoms of ischaemia due to blood vessel stenosis or thrombus formation within a vessel. An unknown, yet identified antigen, is thought to initiate an autoimmunological response in a genetically susceptible patient, where mononuclear infiltration in the vasa media leads to granulomatous inflammation resulting in medial thickening, intimal proliferation and obliteration of elastic layers and medial smooth muscles with cellular infiltration around the vasa vasorum.

Disease progression causes tunica media destruction, often with resultant aneurismal formation or acute aneurismal dissection of affected arteries. The epidemiological distribution of TA is worldwide with the highest prevalence occurring in the Asian population. The disease is more prevalent in younger females with a female to male ratio of 4-9: 1. TA may show heterogeneous disease expression, patterns of arterial involvement and prognosis in different parts of the world. Available data on the African continent and specifically South Africa is limited. The largest study on adults with TA in SA was done in the Western Cape Province at Groote Schuur Hospital. Case reports have been documented in South Africa and Africa. Published literature in South Africa mainly has been focused on TA in the paediatric population group, and, in the Free State Province of South Africa, no published literature has been found. Clinical manifestations are variable, ranging from initially asymptomatic to vague and non-specific symptoms. As the disease progresses, classical features of TA begin to emerge with ischemic symptoms being a prominent feature. The classification of TA requires at least three of the six criteria of the American College of Rheumatology of 1990 to be present. There is often a delay in the diagnosis due to non-specific symptoms and variable clinical presentation.

The diagnosis is often missed due to low clinical awareness and suspicion. No standardized criteria to assess disease activity have been formalized, further contributing to the difficulty in managing the disease. Thus far, no definitive biomarker has been found to diagnose TA. Imaging is paramount to making the diagnosis, establishing the extent of arterial involvement, and assessing disease progression and response to treatment. Computerized tomography angiography (CTA) or Magnetic resonance angiography (MRA) or is used to establish the diagnosis of TA. CTA is most often used in our setting due to restrictions to the accessibility of MRI. CTA and MRA are beneficial for assessing the aorta and its main branches. Treatment for TA can be subdivided into medical and surgical treatment. The ultimate goal of treatment is to suppress the vascular inflammatory process. The natural history and prognosis of TA remains poorly defined. This is due to lacking data for long term follow up. Prognosis mainly depends on the development of complications, albeit from the disease itself or as a consequence of medical or surgical treatment. Further important prognostic factors are duration and extent of both vascular and systemic inflammation, late presentation and diagnosis and treatment resistance.

Appendix F

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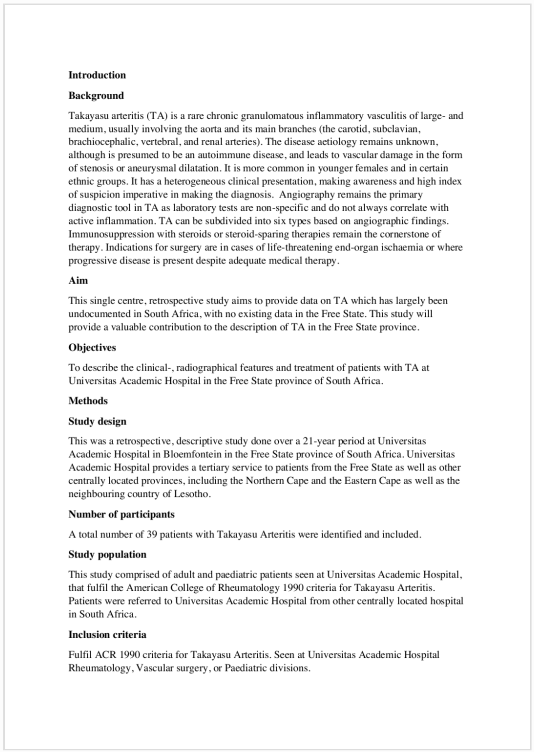

Introduction

Background

Takayasu arteritis (TA) is a rare chronic granulomatous inflammatory vasculitis of large- and medium, usually involving the aorta and its main branches (the carotid, subclavian, brachiocephalic, vertebral, and renal arteries). The disease aetiology remains unknown, although is presumed to be an autoimmune disease, and leads to vascular damage in the form of stenosis or aneurysmal dilatation. It is more common in younger females and in certain ethnic groups. It has a heterogeneous clinical presentation, making awareness and high index of suspicion imperative in making the diagnosis. Angiography remains the primary diagnostic tool in TA as laboratory tests are non-specific and do not always correlate with active inflammation. TA can be subdivided into six types based on angiographic findings. Immunosuppression with steroids or steroid-sparing therapies remain the cornerstone of therapy. Indications for surgery are in cases of life-threatening end-organ ischaemia or where progressive disease is present despite adequate medical therapy.

Aim

This single centre, retrospective study aims to provide data on TA which has largely been undocumented in South Africa, with no existing data in the Free State. This study will provide a valuable contribution to the description of TA in the Free State province.

Objectives

To describe the clinical-, radiographical features and treatment of patients with TA at Universitas Academic Hospital in the Free State province of South Africa.

Methods

Study design

This was a retrospective, descriptive study done over a 21-year period at Universitas Academic Hospital in Bloemfontein in the Free State province of South Africa. Universitas Academic Hospital provides a tertiary service to patients from the Free State as well as other centrally located provinces, including the Northern Cape and the Eastern Cape as well as the neighbouring country of Lesotho.

Number of participants

A total number of 39 patients with Takayasu Arteritis were identified and included.

Study population

This study comprised of adult and paediatric patients seen at Universitas Academic Hospital, that fulfil the American College of Rheumatology 1990 criteria for Takayasu Arteritis. Patients were referred to Universitas Academic Hospital from other centrally located hospital in South Africa.

Inclusion criteria

Fulfil ACR 1990 criteria for Takayasu Arteritis. Seen at Universitas Academic Hospital Rheumatology, Vascular surgery, or Paediatric divisions.

Chapter 1 Takayasu Arteritis

by Eugenie Botha

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Chapter 1

Executive summary

Purpose of the study Takayasu arteritis (TA) is a chronic granulomatous inflammatory vasculitis of large and medium vessels of unknown aetiology. It has a predilection for the aorta and its branches, and can affect the brachiocephalic, carotid, subclavian, vertebral, and renal arteries, as well as the coronary and pulmonary arteries. Expression of the disease is variable, often leading to symptoms of ischaemia due to blood vessel stenosis or thrombus formation within a vessel. An unknown, yet identified antigen, is thought to initiate an autoimmunological response in a genetically susceptible patient, where mononuclear infiltration in the vasa media leads to granulomatous inflammation resulting in medial thickening, intimal proliferation and obliteration of elastic layers and medial smooth muscles with cellular infiltration around the vasa vasorum.

Disease progression causes tunica media destruction, often with resultant aneurismal formation or acute aneurismal dissection of affected arteries. The epidemiological distribution of TA is worldwide with the highest prevalence occurring in the Asian population. The disease is more prevalent in younger females with a female to male ratio of 4-9: 1. TA may show heterogeneous disease expression, patterns of arterial involvement and prognosis in different parts of the world. Available data on the African continent and specifically South Africa is limited. The largest study on adults with TA in SA was done in the Western Cape Province at Groote Schuur Hospital. Case reports have been documented in South Africa and Africa. Published literature in South Africa mainly has been focused on TA in the paediatric population group, and, in the Free State Province of South Africa, no published literature has been found. Clinical manifestations are variable, ranging from initially asymptomatic to vague and non-specific symptoms. As the disease progresses, classical features of TA begin to emerge with ischemic symptoms being a prominent feature. The classification of TA requires at least three of the six criteria of the American College of Rheumatology of 1990 to be present. There is often a delay in the diagnosis due to non-specific symptoms and variable clinical presentation.

The diagnosis is often missed due to low clinical awareness and suspicion. No standardized criteria to assess disease activity have been formalized, further contributing to the difficulty in managing the disease. Thus far, no definitive biomarker has been found to diagnose TA. Imaging is paramount to making the diagnosis, establishing the extent of arterial involvement, and assessing disease progression and response to treatment. Computerized tomography angiography (CTA) or Magnetic resonance angiography (MRA) or is used to establish the diagnosis of TA. CTA is most often used in our setting due to restrictions to the accessibility of MRI. CTA and MRA are beneficial for assessing the aorta and its main branches. Treatment for TA can be subdivided into medical and surgical treatment. The ultimate goal of treatment is to suppress the vascular inflammatory process. The natural history and prognosis of TA remains poorly defined. This is due to lacking data for long term follow up. Prognosis mainly depends on the development of complications, albeit from the disease itself or as a consequence of medical or surgical treatment. Further important prognostic factors are duration and extent of both vascular and systemic inflammation, late presentation and diagnosis and treatment resistance.

Methods Patients who met the 1990 American College of Rheumatology criteria for the diagnosis of TA were included in this retrospective study over a twenty-one-year study period from 2000 until 2021. This study comprised of adult and paediatric patients seen at Universitas Academic Hospital, in the city of Bloemfontein, Free State. They were referred to Universitas Academic Hospital, which is a tertiary institution, from other centrally located hospital in South Africa.

The records of patients were reviewed, and data were analysed from the departments Rheumatology, Vascular Surgery and Paediatrics. This included patient demographics (sex, age, and ethnicity), 1990 ACR criteria, clinical features, anatomical classification, surgical interventions, medical treatment, response to therapy, complications, and outcome. Patients were excluded if there were missing data on clinical features, if no imaging studies were performed and if they had an alternate diagnosis.

Key results The mean age at presentation was fourteen years (9-23), with 71.8% (n= 28) female patients, and this correlates with previous studies on sex predominance and age characteristics. The cohort constituted of 71.8% (n=28) patients of Black African ethnicity and 28.2% (n=11) patients of coloured ethnicity. There were no patients of white, Indian, or Asian ethnicities included. The most common clinical features at presentation were cardiac disease (61.5%, n=24), hypertension (56.4%, n=22) and cerebrovascular disease (48.7%, n=19). 17.9% (n=7) and 15.8% (n=6) of patients presented with peripheral vascular disease and constitutional symptoms, respectively. Gastrointestinal, respiratory, and dermatological manifestations were only present in 5.1% (n=2), respectively. Angiography demonstrated the abdominal aorta to be the most frequently involvement (71.8%, 28/39), followed by common carotid artery lesions (58.9%, 23/39), subclavian artery lesions (56.4%, 22/39) and thoracic aorta lesions (48.7%, 19/39). Therefore, Numano type IV was most commonly found in this study followed by Numano type I and type IIa. Type III and Type IIb was the least common. Stenotic lesions were more common than aneurysmal disease. 94.7% (n=36) of patients were treated with glucocorticoids (GCs). 68.4% (n=26) were combined with Methotrexate and 23.7% (n=9) with Azathioprine. 31,6% (n=12) received Cyclophosphamide 2.6% (n=1) were treated with Mycophenolate Mofetil (MMF). No patients were treated with biologics. Surgical interventions comprised mainly of open surgical procedures.

Conclusions This study revealed that TA, which is a large vessel vasculitis, remains rare, and improving awareness is important for making an early diagnosis and preventing morbidity and mortality. The aetiology remains uncertain although an autoimmune process is implicated. Demographical data and clinical features remain comparable to previous studies worldwide and in previously done South African studies. Cardiovascular and cerebrovascular manifestations were the most frequently seen and lead to significant morbidity. Immunosuppression remains the mainstay of treatment with all patients on glucocorticoids during the course of treatment. Glucocorticoids were still heavily relied upon in the treatment of these patients.

Recommendations Future studies can be done to focus on ways in identifying patients with Takayasu arteritis earlier and exploring to identify novel biomarkers for use in diagnosis and disease activity assessment. Future research on individuals who were treated with biologics earlier in the course of their disease will be crucial to making improvements in the

management of this difficult disease and comparing their outcome with patients on conventional disease modifying agents.

Keywords

Takayasu arteritis; vasculitis; granulomatous inflammation; young female; clinical and radiographic findings

Chapter 1

Literature review

Introduction

The different group of systemic inflammatory illnesses known as vasculitides is characterised by inflammation and, consequently, blood vessel destruction. This ultimately results in ischemia and damage to the tissues or organ supplied by the affected blood vessels.

Any type, size or site of blood vessel may be involved. Vasculitis can be primary/idiopathic or secondary due to another underlying disease. The inflammation can be limited to a single organ, or it can affect multiple organs concurrently. The size of the affected blood vessel classifies the vasculitides into large-vessel vasculitis, medium-vessel, and small-vessel vasculitis. Available literature on TA focuses on describing the clinical features and management of the disease. These prior studies highlight that TA is still of unknown aetiology with often late and advanced presentation. Most of the data originates from Asia with sparse data available on a sub-Saharan population and specifically South Africa (5). No data are available about TA in the Free State.

Multiple authors have attempted to correlate the pattern of disease involvement to their population demographic (2)(5)(6). Variation in pattern of disease has been demonstrated in some studies, with comparative study showing Japanese patients having disease more frequently of the aorta arch and its branches than Korean and Indian patients who had disease of the abdominal aorta (7).

TB (tuberculosis) has been postulated as a possible aetiology, which is of particular interest in the South African context, keeping in mind the high burden of disease in South Africa (8)(9). It is difficult to establish a causal relationship between TB and TA. With high

prevalence of TB in South Africa, the implication may be an incidence higher to other countries where TB is not endemic, which has not been established.

Background and History

Earliest published data about TA dates back as far as 1830. Mikito Takayasu, Ophthalmologist at Kanazawa University in Japan, presented the clinical scenario of a woman with distinct abnormal retinal vascular findings in 1908 (1). Thereafter, Takayasu's colleagues, Katsutomo Ohishi, and Tsurukichi Kagoshima, in a later academic discussion, described the more typical cases of patients with absent pulses (1)(2)(3).

In 1939, Yasuzo Shinmi, coined the term 'Takayasu's Arteritis'(TA), after more cases were reported in Japan. Then in 1951, surgeons at Tokyo University, Kentaro Shimizu and Keiji Sano, introduced TA to the Western world as pulseless disease. A publication on TA by Whiteman and Caccamize in the American Heart Journal, in 1952, led to the spread of knowledge on TA into Western nations (4).

Internists, Ross and McKusick, outlined over 100 cases where decreased or absent pulses in the arms and neck were found, and called this disease entity 'aortic arch syndrome'. They recognised the cases according to the cause of disease as either syphilitic, congenital abnormality, atherosclerotic or traumatic. They cited four cases in their case series as 'young female arteritis', noting these patients as having characteristic ocular and cerebral vascular findings (4).

In 1963, Professor Hideo Ueda, Internist at Tokyo University, studied cases of TA and confirmed pan aortitis involving the aorta and its primary branches and referred to it as 'pan aortitis syndrome'. Professor Ueda postulated an autoimmune aetiology and later renamed it 'aortitis syndrome' to avoid confusion of involvement of the whole aorta (4). In 1975, in honour and recognition of Takayasu as first reporting the disease entity, the Department of Health and Welfare in Japan's research committee proposed naming the disease 'Takayasu Arteritis' (4).

Definition

Takayasu arteritis (TA) is a chronic granulomatous inflammatory vasculitis of large and medium vessels of unknown aetiology (10) (11). It has a predilection for the aorta and its primary branches including the brachiocephalic, carotid, subclavian, vertebral, and renal arteries, in addition to occasionally affecting the coronary and pulmonary arteries. Expression of the disease is variable, often leading to symptoms of ischaemia due to blood vessel stenosis or thrombus formation within a vessel. Disease progression causes tunica media destruction, often with resultant aneurismal formation or acute aneurismal dissection of affected arteries.

Characterised histologically as ‘pan-arteritis’, resulting in intimal thickening, obliteration of medial elastic layers and medial smooth muscles, inflammatory cellular infiltration in the media with infiltration around the vasa vasorum.

Epidemiology

TA is distributed world-wide, with the Asian population experiencing the highest prevalence. The disease is more prevalent in younger females with a female to male ratio of 4-9: 1. The incidence in Asian countries is reported as 1 to 2 cases/million per year and an estimated prevalence of 12.9 to 40 cases/million (3).

TA may exhibit heterogeneous disease expression, patterns of vascular involvement and prognosis around the world (12) (13). In contrast to Asia, the incidence has been reported as 0.3 cases/million in the United Kingdom (14). Epidemiologic studies have concluded that TA has been diagnosed in European countries with increasing prevalence, with a reported incidence rate between 0.4 to 1.5 per million (15).

Available data on the African continent and specifically South Africa is limited. The largest study on adults with TA in SA was done in the Western Cape Province at Groote Schuur Hospital. This was a retrospective, descriptive study spanning over 50 years and included 272 patients (16).

Case reports have been documented in South Africa and Africa (17). Published literature in South Africa mainly has been focused on TA in the paediatric population group, and, in the Free State Province of South Africa, no published literature has been found.

Clinical presentation

Clinical manifestations are variable, ranging from initially asymptomatic to vague and non-specific symptoms, to limb claudication, systemic and renovascular hypertension to cerebrovascular accidents.

Non-specific symptoms include fever, malaise, weight loss, myalgia, or arthralgia. As the disease progresses, classical features of TA begin to emerge with ischemic symptoms being a prominent feature. Hypertension due to stenosis of the aorta or renal artery is a common presentation.

The following are disease features:

• Constitutional symptoms: fever, weight loss and fatigue – common in early phase of the disease.

• Arthralgia/ Myalgia: intermittent or continuous and chronic in nature.

• Carotidynia: tenderness on palpation of a carotid artery in 10 to 30 percent of patients.

• Absent or weak peripheral pulse(s): most common at radial arteries and is often asymmetric; unusual cases of acute vessel occlusion occur with limb gangrene or ischemic

ulcerations; however, this is uncommon due to the usual formation of collateral circulation indicating the chronic nature of disease development.

• Claudication: limb claudication is a common presenting symptom. Subclavian steal syndrome can lead to neurological symptoms or syncope related to exercise induced redirection of blood flow to the upper limb. This results from a stenotic lesion proximal to the origin of the vertebral artery. Other symptoms of claudication include mild to severe upper- or lower limb pain with activity often causing functional impairment.

• Arterial bruit: in patients with stenotic lesions, bruits are audible over the stenosed vessels. Signs and symptoms of aortic stenosis or aortic incompetence can also be present with resultant heart failure in some cases.

• Blood pressure discrepancy between the arms.

• Hypertension: due to coartation of the aorta or renal artery stenosis.

• Angina pectoris: myocardial ischemia can occur due to stenosis of the coronary artery ostia from aortitis or coronary artery inflammation with coronary arteritis. This can lead to myocardial infarction and in complications related to myocardial infarction including mechanical complications (free wall rupture of the left ventricle, interventricular septum rupture, secondary severe mitral regurgitation); pericardial complications; conduction abnormalities; left ventricular dysfunction and left ventricular aneurysm.

• Mesenteric artery ischemia with involvement of abdominal aorta causing post-prandial pain, diarrhoea, and gastrointestinal haemorrhage.

• Skin lesions resembling pyoderma gangrenosum or erythema nodosum.

• Neurological involvement: involvement of the vertebral and carotid arteries with sequelae of decreased cerebral blood flow- dizziness, syncope, transient ischaemic attack, and stroke. A late manifestation of severe disease is visual impairment.

• Respiratory manifestations include dyspnoea, chest pain, haemoptysis, and pulmonary hypertension.

Diagnosis

Takayasu arteritis classification requires that three of the six criteria of the American College of Rheumatology of 1990 be present. The ACR criteria for TA are:

1. Age of onset before 40 years old.

2. Limb claudication.

3. Reduced pulse in the brachial artery.

4. A systolic pressure difference of more than 10 mmHg between two limbs.

5. A bruit in the aorta or subclavian arteries.

6. Angiographic evidence of narrowing or occlusion of the aorta, its primary branches, or large arteries in the proximal upper or lower extremities.

• The sensitivity and specificity of three or more of these six criteria are respectively 90.5% and 97.8%. (10).

• Non-specific symptoms often predominate, especially early on in the course of the disease, as well as variability in clinical presentation and this delays making the correct diagnosis (19).

• The diagnosis is often missed due to low clinical awareness and suspicion (5). No standardized criteria to assess disease activity have been formalized, further contributing to the difficulty in managing the disease. Thus far, no definitive biomarker has been found to diagnose TA (5). Imaging is paramount to making the diagnosis, establishing the degree of arterial involvement, and assessing disease progression and response to treatment (20).

• There is poor correlation between systemic markers of inflammation and inflammation in the vessel wall. There may be active inflammation without elevation of markers of inflammation such as ESR or CRP, and the converse applies. Histological evaluation of arterial specimens of patients in laboratory and clinical remission, may show signs of inflammation. According to the Numano classification, TA is classified into six different subtypes, based on radiographical vascular involvement (5).

• The diagnosis is infrequently made histologically since biopsy of large vessels is impractical (12). However, the diagnosis can be made when an arterial biopsy is available after a revascularizing procedure or repair of an aneurysm.

Assessment of Disease Activity

Disease activity assessment is vital in managing autoimmune diseases. Clinical assessment of disease activity in TA is based on clinical findings, inflammatory markers, and imaging studies (49). Assessing active disease is a challenging task in TA. Unlike other autoimmune diseases, for example rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), where the area of disease is accessible for biopsy, this is not the case for TA. This is due to the inability to obtain a histopathological diagnosis, except in case of vascular biopsy during bypass surgery. Disease extent is extrapolated from the DEI TAK (Disease extent index in Takayasu arteritis) tool, which is a validated tool developed by Indian Rheumatology Association Core Group for Vasculitis (IRVAS), derived from the Birmingham Vasculitis Activity Score (BVAS). The DEI TAK score uses clinical findings in assessing the extent of disease (48).

Imaging modalities used for diagnosis and follow-up:

Computerized tomography angiography (CTA) or magnetic resonance angiography (MRA) is used to confirm the diagnosis of TA. CTA is most often used in our setting due to restrictions to the accessibility of MRA. CTA and MRA are beneficial for assessing the aorta and its main branches. The aorta's structural alterations may be well-characterized anatomically by CTA, but it could possibly fail to identify early disease activity. Although MRA can demonstrate thickening of the artery walls, oedema, and contrast enhancement, it has been

demonstrated that there is little association with clinical activity or systemic inflammation and that its utility for long-term follow-up is limited (13).

Similarly, Colour Doppler Ultrasonography (CDU) is useful for assessing the femoral, axillary, carotid, and temporal arteries, but it does not reflect the thoracic aorta unless it is performed via transoesophageal examination. Similar to CTA and MRA, CDU can detect stenoses, aneurysms, and major artery luminal abnormalities in addition to the characteristic homogeneously thickened vessel walls, mural inflammation, and oedema, which are early signs of inflammation. In addition, CDU offers superior resolution to CTA and MRA. Radiation exposure does not limit the use of MRA or CDU. The overestimation of arterial occlusions, difficulty visualising small branch arteries, and vascular calcifications are all limitations of MRA (13).

The non-invasive imaging technique of positron emission tomography (PET) using 18F-fluorodeoxyglucose (18F-FDG PET) analyses 18F-FDG, which accumulates in hypermetabolic, activated inflammatory cells infiltrating the arteries. The functional data from PET and the anatomical data from CT are combined in 18F-FDG PET/CT. The most accurate diagnosis for early vascular inflammation is 18-FDG-PET (13). Thus, employing PET-CT in the first two phases may allow for the detection of early vascular inflammation as well as the location of such inflammation in the aorta and its branches, which may aid in the early diagnosis of TA. Although it may be difficult to distinguish between atherosclerotic and vasculitic lesions, PET vascular uptake is not vasculitis specific. However, PET cannot distinguish between arterial wall structure and luminal flow; a further drawback of PET-CT imaging is the substantial radiation dose (13).

The Numano classification classifies the disease into 6 types based on radiographic involvement:

Type 1: Branches from aortic arch

Type 2a: Ascending aorta, aorta arch and its branches

Type 2b: Ascending aorta, aortic arch, its branches and descending thoracic aorta

Type 3: Thoracic descending aorta, abdominal aorta and or renal arteries

Type 4: Abdominal aorta and or renal arteries

Type 5: Combined features of 3 and 4.

Differential diagnosis includes:

- Other primary vasculitides (Kawasaki's disease, Polyarteritis Nodosum and Buerger's disease).
- Atherosclerosis and arteriolosclerosis
- Hypercoagulable states (thrombotic thrombocytopenic purpura, antiphospholipid syndrome)
- Congenital (aortic coartation, middle aortic syndrome)

- Vasospastic disorders (posterior reversible encephalopathy syndrome and reversible cerebral vasoconstriction syndrome)
- Infectious causes (cytomegalovirus, herpes virus, hepatitis viruses, HIV, tuberculosis, syphilis, Staphylococcus aureus)
- Malignancies (leukaemia, lymphoma, glioma)
- Immunodeficiency disorders
- Iatrogenic (post radiation therapy)
- Autoimmune secondary vasculitis (SLE, sarcoidosis)
- Renal disorders
- Drugs (cocaine, sympathomimetics)
- Livedoid vasculopathy
- Inherited disorders (Marfan's syndrome, Ehlers-Danlos, neurofibromatosis type I)
- Fibromuscular dysplasia

Pathogenesis

Although the exact aetiology of TA is unknown, the underlying pathology is inflammatory in nature with possible underlying autoimmune disease. This is supported by the finding of elevated levels of cytokines in the sera of patients with TA (46). The antigen or antigens that could trigger the autoimmunity have not been identified yet, however, it has been postulated that a viral or bacterial antigen initiates or produces, through molecular mimicry, the autoimmune process in TA (46). The concept of the "vascular microbiome" has been known for some time, where commensal microorganisms in the blood vessels of healthy patients differ from those of patients with pathological vasculature and vasculitides. Therefore, alteration in the vascular microbiome, called "dysbiosis" could lead to the pathogenesis of TA (47). The disease is characterised by pan-mural involvement with cellular infiltration and intimal proliferation. Activation of vasa vasorum endothelial cells and recruitment of lymphocytes is involved in the pathological process of TA (35).

Natural killer (NK) cells, macrophages, neutrophils, CD4+ T cells, CD8+ T cells, T cells, and inflammatory cells invade the vasa vasorum (11) (21). T-cells, NK cells, and macrophages are the primary drivers of TNF-α production. TNF-α plays an essential part in the formation of granulomas (22) (23). By producing perforin and the killer cell lectin-like receptor subfamily K (NKG2D), T- and NK cells are involved in the death of endothelial cells, according to histopathological analysis of samples of aortic tissues (24).

Acute inflammation results from the release of perforin and other mediators by T and NK cells that express NKG2D receptors upon recognizing MHC1A (the major histocompatibility class I chain-related A) on vascular smooth muscle cells. The natural killer and T-cells also release pro-inflammatory cytokines, which stimulate the production of matrix metalloproteinase (MMPs) and enhance the inflammatory response. The major histocompatibility complex (MHC) antigen increases as a result, and more mononuclear cells are attracted into the vascular wall. Patients with TA were observed to have peripheral T-cells that were active and had a higher CD4/CD8 ratio, indicating that T-helper cells predominated in these patients (25).

Th1 lymphocytes produce interferon-γ, which activates macrophages and causes the release of vascular endothelial growth factor (VEGF), resulting in the formation of giant cells. Increased neovascularization and platelet-derived growth factor (PDGF) release are brought on by VEGF. Smooth muscle migration into the intima and intimal proliferation are the process's ultimate endpoints. By the stimulation of invading neutrophils, Th17 cells produced by the IL-23 milieu also contribute to vascular lesions (26). The contribution of TA pathogenesis by B-cells is still debated.

Patients with TA have reportedly been shown to have anti-aorta antibodies and anti-epithelial cell antibodies (AECA) (27). Systemic vasculitis constitutes only one of the clinical diseases where AECAs have been found. There is an abundance of data to suggest that AECAs cause vasculitis, activate endothelial cells, and cause apoptosis (28). Moreover, it has been reported that TA patients frequently exhibit antiphospholipid antibodies, particularly those against cardiolipin, annexin V, and 2 glycoprotein I. (29). It is still unknown if these antibodies contribute to the pathogenesis of TA.

Other antibodies found in the sera of TA patients include anti-human heat shock protein60/65 autoantibodies (30). None of these, however, have demonstrated specificity to TA. IL-6, IL-8, IL-16, and IL-18 levels have been found to be increased in TA patients, and IL-18 and IL-16 levels are positively correlated with disease activity (31). The correlation between TA and HLA alleles raises the possibility that genetic factors contribute to the aetiology of TA. HLA-B*52 is the only gene that exhibits an association with TA outside ethnicity, according to an analysis of these genetic factors within as well as outside the HLA domain (32).

Two separate susceptibility loci within the HLA region, HLA-DQB1/HLA-DRB1 and HLA-LAB/MICA, have been found and confirmed by a recent large-scale genetic association study that included patients from Turkey, North America and Europe . This study found that patients from North America and Europe similarly had a connection between TA and HLA-B*52 (33). Recent studies have revealed that TA has a number of non-HLA susceptibility loci (15).

Treatment

Treatment for TA can be subdivided into medical and surgical treatment. The ultimate goal of treatment is to suppress the vascular inflammatory process. In cases with life-threatening arterial stenosis or marked aneurysmal formation, open surgical procedures or endovascular procedures are further treatment options to be considered. As a general rule, surgical interventions should only be performed after suppression of inflammation by appropriate and adequate medical therapy (34). Therefore, to optimally treat TA, adequate assessment of disease activity by clinical and radiological evaluation should be performed.

The EULAR consensus definition of active disease is as follows:

1) The presence of typical signs or symptoms of active LVV (large vessel vasculitis).

2) Additionally, at least one of the following:

a. Active inflammation on imaging or tissue biopsy.

b. LVV ischaemic complications.

c. Persistently elevated inflammatory markers (other causes excluded (35).

Medical treatment

Glucocorticosteroids (GC) form the cornerstone of initial immunosuppressive (IS) therapy. Conventional second line treatment consists of Methotrexate, Mycophenolate mofetil, Leflunomide and Azathioprine, as monotherapy or combined with GC to enable tapering of the GC dose.

Cyclophosphamide is also an option but is usually reserved for severe or refractory cases, due to the well-known long term adverse effects such as gonadal suppression.

Although there are no universally accepted criteria for the definition of refractory disease in TA, the Turkish Takayasu Arteritis Study Group definition is used to define refractory disease (36):

1. Disease progression despite treatment based on clinical and radiographical evaluation
2. Any of the following characteristics:

    • Prednisone dose >7.5 mg/day after 6 months of treatment, despite administration of conventional IS agents.

    • Persistent disease activity requiring surgery.

    • ≥Three attacks per year.

    • Death due to active disease; and

    • In cases of refractory disease, biological agents such as Rituximab, Tocilizumab, TNF inhibitors and Abatacept can be used. Evidence from observational studies have shown that biological agents are effective in refractory cases or in cases with disease progression (37).

Surgical treatment

In the late presentation and chronic phases of TA, where vascular lesions are irreversible with medical treatment alone, surgery or endovascular interventions may be considered.

In cases of severe ischemic symptoms of an extremity or severe ischemia to an organ, revascularisation by either endovascular or open surgical intervention may be necessary.

Important indications for surgery are symptomatic cerebral artery stenosis causing cerebrovascular ischemia; coronary artery ischemia; abdominal aorta aneurysm and aortic bifurcation disease with lower limb claudication and ischemia; hypertension caused by renal artery stenosis; severe aortic regurgitation and severe stenosis of the aorta arch (38)(39)(40)(41).

Pregnancy and Fertility

Obstetric complications are more common in women with TA (50). Pre-conception counselling and planning is therefore imperative for a favourable pregnancy outcome. Pregnancy is generally not associated with disease progression, nevertheless, pregnant patients should be managed in a high-risk maternal unit. Complications posing maternal risk are attributable to systemic hypertension leading to the development of complications such as pre-eclampsia, worsening of chronic hypertension, heart failure and strokes. Foetal complications such as growth restriction are because of impaired placental blood flow secondary to uncontrolled hypertension and involvement of the abdominal aorta. Another reason for growth restriction is stenosis of the renal arteries with increased production of renin, causing increased blood pressure (42). Fertility is not directly affected by TA; however, counselling about the risks of teratogenicity of certain immunosuppressive drugs is necessary (42).

Complications and Prognosis

The natural history and prognosis of TA remains poorly defined. This is due to paucity of data for long term follow up. Prognosis mainly depends on the development of complications, albeit from the disease itself, or because of medical or surgical treatment. Further important prognostic factors are severity and extent of systemic and vascular inflammation, late presentation and diagnosis and treatment resistance (4).

Other contributors to poor prognosis include aortic regurgitation, aortic aneurysm, the presence of renal artery stenosis with renovascular hypertension, Takayasu retinopathy, and co-morbidities as a consequence of corticosteroid treatment (4). Hypertension as well as accelerated atherosclerosis due to chronic inflammation are important complications which need early identification and treatment (43). An important complication post-surgery is in-stent stenosis (44). Progressive vessel wall fibrosis and calcification resulting in external stent compression, has been postulated to contribute to this complication.

Mortality in patients with TA are usually related to strokes, aneurysm rupture, myocardial infarction, renal failure and renal failure (45).

Chapter 1 Takayasu Arteritis

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by Eugenie Botha

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Submission ID: 2036265788
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Introduction

Background

Takayasu arteritis (TA) is a rare chronic granulomatous inflammatory vasculitis of large- and medium, usually involving the aorta and its main branches (the carotid, subclavian, brachiocephalic, vertebral, and renal arteries). The disease aetiology remains unknown, although is presumed to be an autoimmune disease, and leads to vascular damage in the form of stenosis or aneurysmal dilatation. It is more common in younger females and in certain ethnic groups. It has a heterogeneous clinical presentation, making awareness and high index of suspicion imperative in making the diagnosis. Angiography remains the primary diagnostic tool in TA as laboratory tests are non-specific and do not always correlate with active inflammation. TA can be subdivided into six types based on angiographic findings. Immunosuppression with steroids or steroid-sparing therapies remain the cornerstone of therapy. Indications for surgery are in cases of life-threatening end-organ ischaemia or where progressive disease is present despite adequate medical therapy.

Aim

This single centre, retrospective study aims to provide data on TA which has largely been undocumented in South Africa, with no existing data in the Free State. This study will provide a valuable contribution to the description of TA in the Free State province.

Objectives

To describe the clinical-, radiographical features and treatment of patients with TA at Universitas Academic Hospital in the Free State province of South Africa.

Methods

Study design

This was a retrospective, descriptive study done over a 21-year period at Universitas Academic Hospital in Bloemfontein in the Free State province of South Africa. Universitas Academic Hospital provides a tertiary service to patients from the Free State as well as other centrally located provinces, including the Northern Cape and the Eastern Cape as well as the neighbouring country of Lesotho.

Number of participants

A total number of 39 patients with Takayasu Arteritis were identified and included.

Study population

This study comprised of adult and paediatric patients seen at Universitas Academic Hospital, that fulfil the American College of Rheumatology 1990 criteria for Takayasu Arteritis. Patients were referred to Universitas Academic Hospital from other centrally located hospital in South Africa.

Inclusion criteria

Fulfil ACR 1990 criteria for Takayasu Arteritis. Seen at Universitas Academic Hospital Rheumatology, Vascular surgery, or Paediatric divisions.

Exclusion criteria

Missing data on clinical features or CT angiography not performed. Uncertainty of diagnosis or disease due to secondary causes.

Ethical considerations

Ethical approval was obtained from the Health Sciences Research Ethics Committee with approval number **UFS-HSD2022/0116/2908**.

Results

Thirty-nine patients with Takayasu arteritis were identified. The medical records of these 39 identified patients were reviewed. Most patients were female (71.8 % n= 28). 71.8 % of patients were of Black African ethnicity (n= 28) and 28.2% (n= 11) were coloured. Median age at presentation was fourteen years (IQR 9,23), all participants were less than forty years old. Twenty-four patients (61.5 % n=24) presented with cardiac disease, twenty-two (56.4%) with hypertension and nineteen (48.7%) with cerebrovascular disease. 17.9% and 15.8% of patients presented with peripheral vascular disease and constitutional symptoms, respectively. Gastrointestinal, respiratory, and dermatological manifestations were only present in 5.1% of patients.

Table 4 depicts vessel involvement in this study:

Vertebral artery stenosis 34.6% (n=9); Common carotid artery stenosis 64.7% (n=22); Brachiocephalic artery stenosis 37% (n= 10); Subclavian artery stenosis 52.9% (n=18); Aorta arch stenosis 28.1% (n=9); Ascending aorta stenosis as well as aneurysm were equally seen 19.4% (n=6); pulmonary arteries were not involved in 72% (n=18) of cases; Thoracic aorta stenosis 38.2% (n= 13); Abdominal aorta stenosis 55.3% (n=21); Renal artery stenosis 47.4% (n=18); Mesenteric artery stenosis 29.4% (n=10); Iliac artery stenosis 18.8% (n=6).

Abdominal aorta involvement was the most frequent (71.8%, 28/39), followed by common carotid lesions (58.9%, 23/39), subclavian artery lesions (56.4% , 22/39), thoracic aorta lesions (48.7%, 19/39), renal artery lesions (46.1%, 18/39), aorta arch lesions (35.8%, 14/39), ascending aorta lesions (30.7%, 12/39), mesenteric artery lesions (28.2%, 11/39), brachiocephalic artery lesions (25.6%, 10/39), vertebral artery lesions (23%, 9/39), iliac artery lesions (17.9%, 7/39) and pulmonary artery involvement (15.3%, 6/39).

94.7% of patients were treated with glucocorticoids (n=36). 68.4% (n=26) were combined with Methotrexate and 23.7% (n=9) Azathioprine. 31,6%(n=12) were treated with Cyclophosphamide. 2.6% (n=1) was treated with Mycophenolate Mofetil (MMF). No patient was treated with Leflunomide, Cyclosporine, Rituximab, or other biologics.

Equal percentage of patients, 37.5% (n=12) showed improvement on therapy or remained stable on treatment. Twenty-five percent (n=8) had disease progression.

Complications seen were stroke in 35.5% (n=11), cardiac failure in 41.9% (n=13), renal failure in 19.4% (n=6) and 22.6% (n=7) had other complications related to medical and surgical treatment. Other complications were graft occlusion following open surgery; blindness; opportunistic infections secondary to immunosuppressive therapy and seizures complicating posterior reversible leukoencephalopathy syndrome secondary to severe

uncontrolled hypertension. No patients suffered aneurysm rupture nor myocardial infarction. 71.4% (n=25) of study participants had no surgical intervention. 28.6% (n=10) had surgical management. Nine of these surgeries were open surgical procedures and one was an endovascular procedure. Surgeries included: Mechanical aorta valve replacement with aorta root repair; nephrectomy for non-functioning kidney; aorta-iliac artery bypass; bilateral carotid artery-aorta bypass; bioprosthetic aorta valve; subclavian artery bypass; femoral popliteal artery bypass and forefoot amputation.

The only endovascular intervention performed in this study was percutaneous stenting of a stenosed renal artery. It was unclear whether the four other patients had surgery as no data could be found.

Complications post-surgical intervention found were one patient suffered in-stent stenosis likely secondary to vessel wall fibrosis causing external compression. No patient suffered any neurological sequelae including TIA or stroke.

For the included study period, 75.7% (n=28) were alive on follow-up, one patient had demised and eight (21.6%) were lost to follow-up.

Table 1

Presenting feature	Frequency (n=39)	Percentage (%)
Cerebrovascular	19	48.7
Hypertension	22	56.4
Cardiac	24	61.5
Constitutional	6	15.8
Peripheral vascular	7	17.9
Gastrointestinal	2	5.1
Dermatological	2	5.1
Respiratory system	2	5.1
Other	1	2.6

Table 2

CNS feature	Frequency	Percentage (%)
Cerebrovascular accident	12	63.2
Visual disturbance	6	31.6
Transient ischaemic attack	4	21.1
Carotynia	1	5.3

Table 3

Cardiac feature		Frequency	Percentage (%)
Heart failure		18	69.2
Angina		10	37

Other		9	36
Aorta incompetence		6	24
Aorta stenosis		4	16

Table 4

Anatomical classification Based on radiography	**Aneurysm / Stenosis / Both /None**	**Frequency**	**Percentage (%)**
Vertebral artery	Aneurysm	1	3.8
	Stenosis	9	34.6
	None	16	61.5
Common carotid artery	Aneurysm	1	2.9
	Stenosis	22	64.7
	Both	1	2.9
	None	10	29.4
Brachiocephalic artery	Aneurysm	1	3.7
	Stenosis	10	37
	None	16	59.3
Subclavian artery	Aneurysm	3	8.8
	Stenosis	18	52.9
	Both	2	5.9
	None	11	32.4
Aorta arch	Aneurysm	5	15.6
	Stenosis	9	28.1
	Both	1	3.1
	None	17	53.1
Ascending aorta	Aneurysm	6	19.4
	Stenosis	6	19.4
	Both	1	3.2
	None	18	58.1
Pulmonary artery	Aneurysm	4	16
	Stenosis	3	12
	None	18	72
Thoracic aorta	Aneurysm	2	5.9
	Stenosis	13	38.2
	Both	5	14.7
	None	14	41.2
Abdominal aorta	Aneurysm	3	7.9
	Stenosis	21	55.3
	Both	5	13.2
	None	9	23.7
Renal artery	Stenosis	18	47.4
	Both	1	2.6
	None	19	50
Mesenteric artery	Aneurysm	1	2.9
	Stenosis	10	29.4
	Both	1	2.9

	None	22	64.7
Iliac artery	Aneurysm	1	3.1
	Stenosis	6	18.8
	Both	1	3.1
	None	23	71.9

Discussion

Demographic data

This study comprised of 39 patients who had presented to Universitas Academic Hospital over a 21-year period from 2000 until 2021. Takayasu arteritis has a worldwide distribution, although its prevalence is higher in young females of Asian ethnicity (3)(4)(5). As Espinoza *et al*. and Mandl *et al*. postulates, this higher incidence in Asian populations is due to higher frequency of HLA-B*52 expression in these populations(1)(2).

There were no patients of Asian ethnicity found in this study. Instead, the majority were of Black African or coloured ethnicity. This most likely reflects the ethnic distribution of the South African population and the specific majority ethnicity of patients seen at Universitas Academic Hospital. This is comparable to findings in South Africa by Kaawan *et al*.in their study at Tygerberg Academic Hospital in the Western Cape province(6). They found that 68% of participants were coloured and twenty-four percent were of black ethnicity. Another study done in South Africa by Mwipatayi *et al*. at Groote Schuur Hospital in the Western Cape province, looked at 272 cases over a 50-year study period. In this study 68% of participants were coloured(7). This study showed similar finding to previously documentation of sex distribution where 72% of patients were female(2)(5). The mean age at presentation was 14 years (9-23) and all patients were below 40 years of age (2). This was in line with findings from previous studies. It can also present in childhood and children usually have differences in presentation compared to adults (1). The youngest patient included was four years of age and twelve patients were under ten years of age at the time of diagnosis.

Clinical presentation and diagnosis of Takayasu arteritis

All patients with TA fulfilled the 1990 ACR criteria for classification of TA. Not only had variability in presentation between different ethnic groups been shown, but also recent studies from Korea and Japan have shown differences between males and females. (1)

Clinical heterogeneity prevails in the presentation of patients with this disease(2). This is due to the disease manifestations dependent on the pattern of arterial involvement. The disease classically presents triphasic, with the initial, pre-stenotic phase consisting of vague and non-specific systemic signs and symptoms, the active phase which leads to symptoms relating to arterial occlusion and stenosis and lastly the fibrotic, burnt-out, stenotic phase. Quinn *et al*. found in their study of 275 patients prospectively recruited from the National Institutes of Health (NIH) and Vasculitis Clinical Research Consortium (VCRC), where patients were divided into five clinical categories based on presenting feature at diagnosis, that patients do not necessarily progress through the triphasic phases of the disease(16).

Patients can present with non-specific symptoms reflecting the inflammatory nature of TA complaining of systemic symptoms including fever, myalgias, weight loss and arthralgias. In

this study, 15.8% (n=6), had constitutional symptoms as presenting feature. A study by Khan *et al*., where eighteen patients were studied, found that twenty-two percent had constitutional symptoms at disease onset (8)Danda *et al*. compared clinical features from various cohorts from around the world (2)In this study, the majority of patients presented with cardiovascular system involvement. This was documented to occur in 61.5%. In descending order of frequency: Congestive cardiac failure (69.2%, n=18); angina (37%, n=10); other cardiac involvement (36%, n=9); aorta regurgitation (24%, n=6); aorta stenosis (16%, n=4). Dilated cardiomyopathy was present in the "other" category. The aetiology of the cardiomyopathy was not elucidated, it is reasonable to assume the cause to have been ischaemic or secondary to severe prolonged hypertension. Hypertension is seen in 75% to 80% of cases of TA(10). The pathogenesis of hypertension in TA is multifactorial and complex. Hypertension is usually secondary and most frequently observed due to renal artery stenosis, followed by stenosis of the descending thoracic aorta, abdominal aorta stenosis or severe aorta regurgitation. In the present study, hypertension was seen in 56.4% (n=22) of patients. In comparison, Misra *et al*., who compared the presentation and prognosis of TA with or without ischaemic stroke or transient ischaemic attack (TIA), in a large cohort study in India reported hypertension in 73.5% of patients with stroke or TIA, and present in 81,5% of patients without stroke or TIA(11). No patient in this study had a documented myocardial infarction. Patients in this study with angina did not undergo conventional coronary artery angiography nor CT coronary angiography. The reason likely was that the study patients were not diagnosed with myocardial infarction thus requiring coronary artery angiography. As Huo *et al*. found in their study of 1580 patients with TA, between 2002 and 2021, 5.9% of patients had coexisting myocardial ischaemia and neurological symptoms (12). Neurological involvement comprised of stroke (63.2%, n= 12), visual disturbance (31.6%, n=6), TIA (21.1%, n= 4) and carotidynia (5.3%, n=1). Compared to cohorts from different countries, stroke had higher incidence in this current study. The reason for the discrepancy could be due to a smaller sample size leading to sampling heterogeneity. The risk of stroke is increased in TA and there is also higher risk of recurrent stroke in the event of a previous stroke or TIA(10). A study from the United Kingdom, comparing primary care databases, comparing 142 patients with TA with 1271 age- and sex-matched controls, found that 13.4 % of the TA patients had stroke versus 4.9% in the control group (hazard ratio 4.38, 95% confidence interval, 2.24-8.55)(10). Haemorrhagic as well as ischaemic stroke can occur in TA. Haemorrhagic stroke usually occurs as consequence of severely uncontrolled hypertension. In the present study, only ischaemic stroke was seen. Stroke and TIA in TA can occur due to involvement of intracranial or extracranial vessels as well as, a consequence of vascular surgery procedures. In this study, patients presented with or developed stroke or TIA during follow-up and not as a consequence of vascular surgery. No patient in this study had recurrent strokes or TIA's.

Diagnosing TA can be challenging due to non-specific symptoms often predominating early in the course of the disease. It is therefore imperative that clinicians have a high index of suspicion when patients present with possible large vessel vasculitis. Diagnosis of TA is made with clinical findings and supported by imaging studies and laboratory data. In 1990, the American College of Rheumatology (ACR) developed classification criteria for TA based on the presence of six clinical criteria with the diagnosis made when three out of six criteria were met, with a sensitivity of 90.5% and specificity of 97.8%(14). These criteria were used as inclusion criteria for patients in this study.

In 2022, new classification criteria were developed and validated for use in research by the ACR/EULAR (15). These criteria are intended to use in classification of vasculitis and not to be used to diagnose vasculitis. This classification criteria aims to distinguish TA from TA mimics. These criteria include ten clinical features, a score of five or more is required to diagnose TA. Critique for the 1990 ACR classification criteria of TA was that these criteria were developed using 63 patients with TA, exclusively from North America, excluding patients from Asia as well as Europe, compared to 744 healthy controls. Pattern of arterial disease differs in these populations(15). An update on these criteria were necessary to include a wider geographical demographic and a larger patient population. The new criteria have a sensitivity of 93.8% and specificity of 99.2%.

Furthermore, delay in making the diagnosis of TA worsen outcomes and leads to substantial morbidity. Factors that contribute to significant morbidity in TA are congestive cardiac failure and neurological ischaemic events such as stroke and TIA (18). Possible reasons for delay in diagnosing TA could be an alternative diagnosis made initially or patients presenting late in the course of the disease.

Disease extent and activity scores were not used in this study to quantify active disease. This is since these scoring tools were not used in the Rheumatology department. Mortality in TA is related to complications such as stroke, renal failure, heart failure or aneurysm rupture. One patient had died of unknown cause.

Role of Non-Invasive Imaging

Diagnostic imaging modalities used to delineate the arterial involvement in TA are CTA, MRA, PET CT, PET MRI, and colour doppler ultrasound (CDU). Each of these imaging modalities have their respective strengths and limitations for use. The main disadvantage of CTA is the high dose of ionising radiation used as well as limitations in CTA for follow-up due to the radiation exposure and other contraindications with contrast usage(2).

Computer tomography angiography (CTA) was used in this study to evaluate vascular involvement. Magnetic resonance angiography (MRA) remains the gold standard for radiological diagnosis of TA, however, due to lack of availability of MRA, ease of access, and long waiting periods for MRA, CTA was used to diagnose TA. No patient in this study had MRA imaging performed. CTA reveals narrowing of the arterial lumen and aneurysmal lesions with vital information on the vessel wall. This includes features such as wall thickening and calcification and effect of contrast enhancement.

Response to therapy is monitored with repeat angiographic imaging, initially six to twelve monthly during the first two years on treatment and thereafter yearly. In Tombetti and Mason's prospective study, patients on treatment were followed up with MRA for a median of eighteen months. They concluded that 40% of arterial lesions remained stable, 37% showed disease progression and twenty-three percent showed improvement on treatment. Based on the response, assessed clinically, with laboratory parameters of inflammation and with imaging, GCs can be tapered to ≤ 5mg per day, with careful and systematic patient monitoring for relapse. Relapse is common after tapering or stopping IS therapy.

Comarmond *et al*. concluded in their French study, including 318 patients, over a 44-year study period, that 50% of patients will suffer relapse and suffer a vascular complication within ten years of diagnosis(17).

Angiographic findings

Abdominal aorta involvement was the most frequent (71.8%, 28/39), followed by common carotid lesions (58.9%, 23/39), subclavian artery lesions (56.4%, 22/39) and thoracic aorta lesions (48.7%, 19/39).

Therefore, Numano type IV was most commonly found in this study followed by Numano type I and type IIa. Type III was the least common. Cluster one was therefore the most abundant in this study.

Recently, Goel *et al*.'s cluster analysis strategy, classified patients into three distinct subsets using the pattern of arterial involvement. Patients in cluster one have more vascular disease in the abdominal aorta, renal and mesenteric arteries. Patients in cluster two have bilateral disease in the carotid and subclavian arteries and cluster three patients usually have asymmetrical disease in fewer vascular territories(18).

Treatment

Immunosuppression (IS) has remained the cornerstone of treatment for TA. TA requires long term immunosuppressive therapy and has a high relapse rate on tapering or stopping of IS. Clinical remission is the ultimate goal of therapy, but this is not always achieved in patients with TA. Induction is usually achieved with high dose glucocorticoids (GC), 1mg/kg/day, combined with conventional disease-modifying anti-rheumatic drugs (cDMARDs). The most frequently used combination was GC with Methotrexate (MTX), followed by Azathioprine (AZA). Cyclophosphamide (CYC) was used only in paediatric patients included in this study. CYC is usually reserved for patients who present with severe, life-threatening disease or relapse on conventional IS therapy. Biological therapies have emerged as promising treatment strategies where patients relapse on cDMARDs or show progressive disease despite adequate immunosuppression. Biological therapy was not used on any patients in this study.

Surgery in TA can be considered when medical therapy has failed or when the disease remains refractory with severe end-organ ischaemia. A recent study in 2020 by Porter *et al*. concluded that patients with symptomatic cerebrovascular disease from severe supra-aortic stenosis, improved with biological therapy and did not require surgical intervention(19). Indication for surgical intervention in TA are critical arterial stenosis with end organ damage, aneurysm rupture, severe aortic regurgitation due to aneurysmal dilatation of the aorta root. In-stent stenosis is an important complication post-surgery(21). External stent compression by progressive vessel wall fibrosis and calcification was suggested to contribute to this complication.

The association between chronic inflammatory diseases and increased incidence of cardiovascular disease and accelerated atherosclerosis has clearly been established, therefore it is of vital importance that cardiovascular risk management be addressed(16).

Study Limitations

The following study limitations are to be considered and include, small sample size, single centre experience and non- standardisation in obtaining clinical and radiographical data. This was due to clinical data not comprehensively recorded by colleagues and differences in reporting of radiology reports.

Recommendation for future studies

Future studies can be done to focus on ways in identifying patients with Takayasu arteritis earlier and exploring to identify novel biomarkers for use in diagnosis and disease activity assessment. Progress in the management of this challenging disease will depend on the future study of patients treated with biologics earlier in the course of the disease and comparing their outcome with patients on conventional disease modifying agents.

Conclusion

Takayasu arteritis remains a rare albeit relevant disease of young females leading to significant morbidity and mortality if the diagnosis is delayed. The diagnosis of TA is often missed due to low clinical awareness and variable clinical presentation. Diagnosing TA remains challenging. Thus far, no biological marker specific to TA has been identified. No standardised criteria exist to assess disease activity, further contributing to the difficulty in managing the disease. Imaging is paramount to making the diagnosis, establishing the extent of arterial involvement, and assessing disease progression and response to treatment. Immunosuppression with combination cDMARDs remains the mainstay of treatment. Surgery is indicated in certain clinical scenarios. Early and timely access to biologics in refractory or relapsing disease can negate the need for surgical intervention and might have an effect on morbidity and mortality. This study provides a valuable contribution to the body of knowledge about TA in the South African setting with the first study done on patients from the Free State province.

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MASTER OF MEDICINE

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DATE OF MEETING	25 November 2021

DEPARTMENT	Internal Medicine
STUDENT NUMBER	2007020643
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TITLE OF THE RESEARCH PROJECT
An Overview of Takayasu Arteritis at and Academic Hospital in Central South Africa.

WM Simmonds
RESEARCH COORDINATOR

24-FEB-2022
DATE

BJJ VAN RENSBURG
SUPERVISOR(S)

24-Feb-2022
DATE

HEAD OF THE DEPARTMENT

25-feb 2022
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Appendix H

Manuscript preparation South African Medical Journal

Preparing an article for anonymous review

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Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

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- Abbreviations should be spelt out when first used and thereafter used consistently, e.g., 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.
- Scientific measurements must be expressed in SI units except blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g., 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g., '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g., μ not u for micro, a not for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e., 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g., TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors with regards to the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g., '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counsellors. J Genet Counsel 2008; 17:424-433: standard human pedigree nomenclature.

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text. Do not replicate data in tables and in text.

Structured abstract

- This should be 250-400 words, with the following recommended headings:

o **Background:** why the study is being done and how it relates to other published work.

o **Objectives:** what the study intends to find out

o **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

o **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.

o **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g., primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled and describe selection and exclusion criteria.

- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g., what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author

- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e., not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others. [3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.

- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:

o On the CrossRef homepage, paste the article title into the 'Metadata search' box.

o Look for the correct, matching article in the list of results.

o Click Actions > Cite

o Alongside 'URL =' copy the URL between { }.

o Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

• Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

• Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

• Acts:

South Africa. National Health Act No. 61 of 2003.

• Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) would indicate Cape, (G) Gauteng, and so on.

NOTE: no. after the v

- *Other references (e.g., reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g., '... (Prof. Michael Jones, personal communication)'.