

## OPHTHALMIC MANIFESTATIONS OF TAKAYASU ARTERITIS IN SOUTH INDIAN POPULATION

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### ABSTRACT

#### BACKGROUND

Takayasu arteritis is a chronic inflammatory vasculopathy mainly affecting the aorta and its main branches and rarely the pulmonary artery. It usually affects females of the childbearing age group and is more prevalent in the South East Asian countries.<sup>1</sup> Ocular manifestations are not uncommon in cases of Takayasu arteritis. They may be ischaemic ocular manifestations when aorta and its branches are involved and get stenosed or hypertensive retinopathy when renal or suprarenal aorta is involved.<sup>2</sup> Uyama and Asayama broadly classified the ocular manifestations into three types.<sup>3</sup> Type 1 comprised of the ischaemic ocular manifestations of Takayasu arteritis, termed as Takayasu Retinopathy which has been further classified into four stages. Stage one is characterised by the distention of veins, stage two consists of microaneurysm formation, occurrence of arteriovenous anastomoses indicates stage three and complications like retinal ischaemia, neovascularisation, rubeosis iridis and vitreous haemorrhage occurs in stage four. Type two ocular findings have features of mixed retinopathy and type three had retinal manifestations due to hypertension which occurs due to the involvement of the renal and abdominal aorta. Since this disease occurs predominantly in younger individuals it causes severe ocular morbidity in the young if not diagnosed and intervened at an early stage.

The aim of this study was to evaluate the clinical spectrum of ocular findings in patients with Takayasu arteritis and to describe the Fundus Fluorescein angiographic characteristics of various retinal findings in patients with Takayasu arteritis.

#### MATERIALS AND METHODS

63 patients who were diagnosed as Takayasu Arteritis who attended our tertiary eye care centre in the time period of November 2014 to march 2017 were included in our study.

#### RESULTS

This cross-sectional study consisted of 63 patients. The mean age of the presentation of the study population was 27.8 years and the mean duration of the disease after which the patient developed eye or eye related symptomatology was 2 years. The commonest ocular manifestation was type 3 Takayasu retinopathy. Other posterior segment manifestations included, Type 1 and Type 3 Takayasu retinopathy, ocular ischaemic syndrome, retinal vasculitis and Anterior ischaemic optic neuropathy. The commonest anterior segment manifestation was posterior sub capsular cataract which was found in 33.3% of the patients. Fundus Fluorescein angiography was performed in 34 patients.

#### CONCLUSION

This study is to highlight the fact that Takayasu arteritis can present with multitudinous ocular manifestations which can be hypertensive or hypoperfusive and can lead to significant ocular morbidity if not for timely intervention. This study is to strongly emphasise routine and regular ophthalmic screening in patients with Takayasu arteritis at the time of diagnosis and also at adequate intervals to diagnose significant treatment related complications like steroid induced cataract at an early stage.

#### KEYWORDS

Takayasu Arteritis, Takayasu Retinopathy, Ischaemic Optic Neuropathy.

**HOW TO CITE THIS ARTICLE:** Arumugam N, Mohankumar A. Ophthalmic manifestations of Takayasu arteritis in South Indian population. J. Evid. Based Med. Healthc. 2017; 4(45), 2769-2774. DOI: 10.18410/jebmh/2017/550

Financial or Other, Competing Interest: None.

Submission 15-05-2017, Peer Review 22-05-2017,

Acceptance 03-06-2017, Published 05-06-2017.

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DOI: 10.18410/jebmh/2017/550



#### BACKGROUND

Takayasu arteritis is a chronic inflammatory vasculopathy mainly affecting the aorta and its main branches and rarely the pulmonary artery. It usually affects females of the childbearing age group and is more prevalent in the South East Asian countries.<sup>1</sup> Ocular manifestations are not uncommon in cases of Takayasu arteritis. They may be ischaemic ocular manifestations when aorta and its branches are involved and get stenosed or hypertensive retinopathy when renal or suprarenal aorta is involved.<sup>2</sup> Uyama and

Asayama broadly classified the ocular manifestations into three types.<sup>3</sup> Type 1 comprised of the ischaemic ocular manifestations of Takayasu arteritis, termed as Takayasu Retinopathy which has been further classified into four stages. Stage one is characterised by the distention of veins, stage two consists of microaneurysm formation, occurrence of arteriovenous anastomoses indicates stage three and complications like retinal ischaemia, neovascularisation, rubeosis iridis and vitreous haemorrhage occurs in stage four. Type two ocular findings have features of mixed retinopathy and type three had retinal manifestations due to hypertension which occurs due to the involvement of the renal and abdominal aorta. Since this disease occurs predominantly in younger individuals it causes severe ocular morbidity in the young if not diagnosed and intervened at an early stage.

**Purpose**

1. To study the clinical spectrum of ocular findings in patients with Takayasu arteritis.
2. To study the Fundus Fluorescein angiographic characteristics of various retinal findings in patients with Takayasu arteritis.

**MATERIALS AND METHODS**

**Subject Selection**

This was a cross sectional study which was conducted at Regional Institute of Ophthalmology and Government Ophthalmic Hospital from November 2014 to March 2017. A total of 63 patients who were diagnosed as Takayasu arteritis were included in the study. Patients with co existent diabetes mellitus, recent history of ocular surgeries were excluded from the study. All the patients underwent detailed ophthalmic evaluation including recording Uncorrected Visual Acuity (UCVA), Best Spectacle Corrected Visual Acuity (BSCVA) using Snellen’s visual acuity chart. Intraocular pressure measurement using Goldman’s applanation tonometer was done. A detailed slit lamp examination and fundus assessment using Slit lamp biomicroscopy with a +90

D lens and indirect ophthalmoscopic examination was performed.

The patients underwent fundus fluorescein angiography when necessary when vasculitis was suspected. It also helped to assess the capillary non-perfusion areas and neovascularisation if any. Optical coherence tomography was also performed when needed to assess the macular status. Monitoring and follow up of patients was done by taking serial fundus photographs of patients using Kowa VX 10 along with routine fundus examinations.

**Follow up-** The patients were referred back to the rheumatologist for the control of systemic parameters. Patients who required emergency stenting or other procedures were referred to the cardiovascular surgeon. Patients were reviewed simultaneously by us for the control of ocular features.

**RESULTS**

This cross sectional study consisted of 63 patients, which comprised of 52 females and 11 males (male: female ratio of 1:4.72). The mean age of the presentation of the study population was 27.8 years (range 20 – 34 years). The mean age at which diagnosis of Takayasu arteritis was made 25.1 years and the mean duration of the disease after which the patient developed eye or eye related symptomatology was 2 years. The median follow up time was 11 months (range 2 – 15 months).

57 patients were known patients of Takayasu arteritis who were referred to our hospital who were referred for ocular symptoms. The remaining six patients came to us with ocular symptomatology and then were found to have Takayasu arteritis. All the six patients were young hypertensives with absent pulses in the lower extremities who were then diagnosed to have Takayasu arteritis with physician opinion. The commonest type of Takayasu arteritis was Type 4 (with the involvement of the abdominal aorta or renal aorta). The general characteristics of the study population are depicted in Table 1.

Type of Takayasu Arteritis	Number of Patients	Male/Female	Mean Age of Diagnosis (Years)	Mean Duration Before Ophthalmic Features (Years)
Type 1	8	1/7	21.2	2.3
Type 2	4	0/4	20.7	1.4
Type 3	10	2/8	29.8	2
Type 4	34	8/26	25.3	3.1
Type 5	7	0/7	22.1	1.2

**Table 1. General Characteristics of the Study Population**

The mean initial visual acuity of our study population was 6/24 (range 6/9 to counting fingers at one meters) and the mean final visual acuity was 6/12 (range, 6/6 to counting fingers at 3 meters). The visual acuity improved by an average of 4.3 Snellen’s lines in 19 patients. There was worsening of visual acuity by 5.7 Snellen’s line in 22 patients, remained the same in 22 patients.

Among our study population, 43 patients had eye related symptoms whereas 20 patients were asymptomatic. Among the symptomatic patients, headache was the commonest (42%) followed by defective vision (37%). Floaters were present in the remaining 21% of patients.

The commonest ocular manifestation was type 3 Takayasu retinopathy which is the hypertensive manifestations in the retina which was found in 34.92%

patients. Other posterior segment manifestations included, Type 1 Takayasu retinopathy which was due to hypoperfusive features was seen in 15.9% of patients. Type 3 Takayasu retinopathy was seen in 6.34 % of the patients. Two patients presented with ocular ischaemic syndrome in which one patient had bilateral presentation. Both the patients had a diagnosis of type 1 Takayasu retinopathy. 8 patients presented with features of retinal vasculitis with features of superficial haemorrhages and Roth spots and vascular staining and leakage depicted in fundus fluorescein angiography. Anterior ischaemic optic neuropathy was found in 6 patients. In six patients the reduction in vision was found to be due to plain refractive error which lead to ocular symptoms which was corrected by best refraction. Four patients were found to have nil ophthalmic findings.

The commonest anterior segment manifestation was posterior sub capsular cataract which was found in 33.3% of the patients. One patient presented with scleritis who upon rheumatologist work up was found to have underlying Takayasu arteritis. Other anterior segment manifestation included iris neovascularisation which was found in one patient with ocular ischaemic syndrome. The ocular findings are summarised in the Table 2.

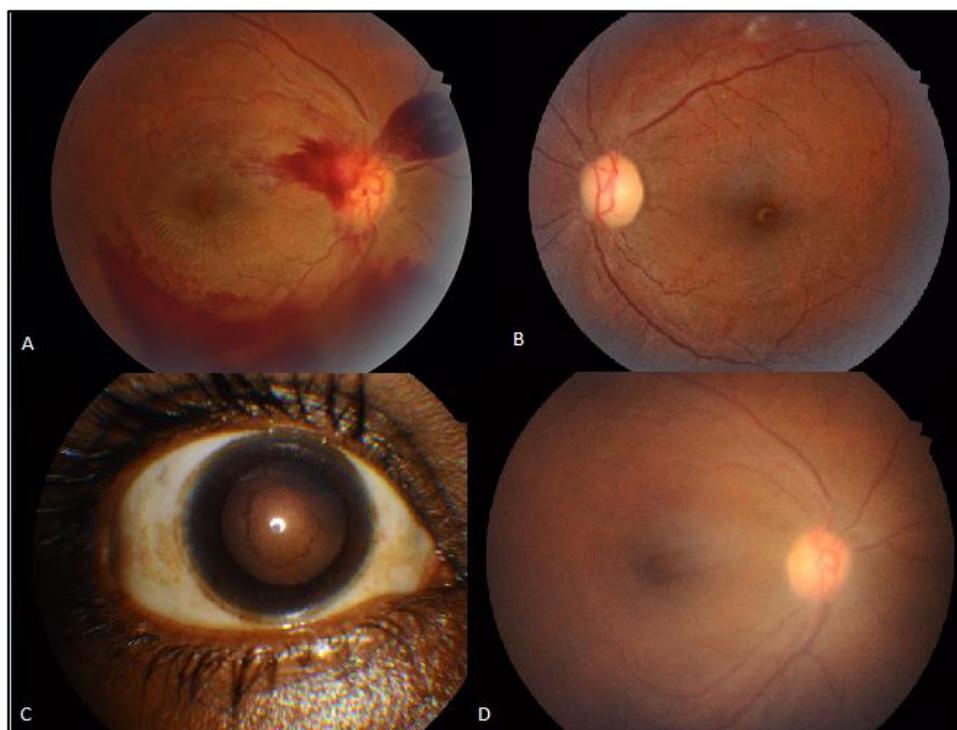
Anterior ischaemic Optic Neuropathy	6
Central retinal artery occlusion	3
No significant finding	8
Anterior Segment Manifestation	
Steroid Induced cataract	24
Scleritis	1
Iris neovascularisation	2
<b>Table 2. Ocular Findings</b>	

Among our study population 34 patients underwent Fundus Fluorescein angiography for the assessment of the retinal changes and also the confirmation of diagnosis. The mean arm to retina circulation time was 27 seconds.

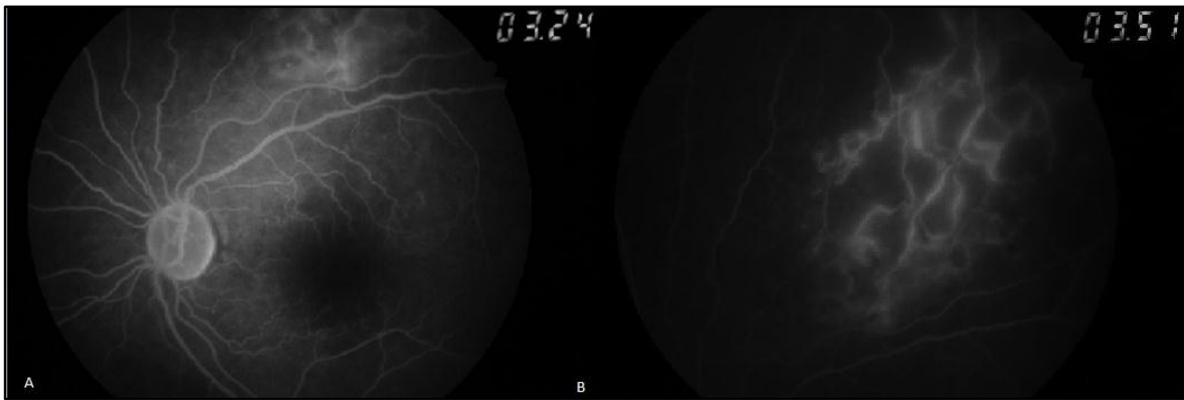
All patients were treated with oral prednisolone (1 mg/kg of body weight). Anti-hypertensives were given to patients with type 4 and 5 Takayasu arteritis. 12 patients who did not have good control with systemic steroid therapy and five patient who showed poor response to steroid therapy were treated with oral mycophenolate mofetil in collaboration with the rheumatologist and cardiothoracic surgeon.

The patients with central retinal artery occlusion, ischaemic optic neuropathy and ocular ischaemic syndrome were considered for stenting and other vascular surgical procedure to improve the visual outcome and reduce the visual morbidity considering the age of the patients (11 patients). The patients with central retinal artery occlusion did not regain any useful vision due to the consecutive optic atrophy.

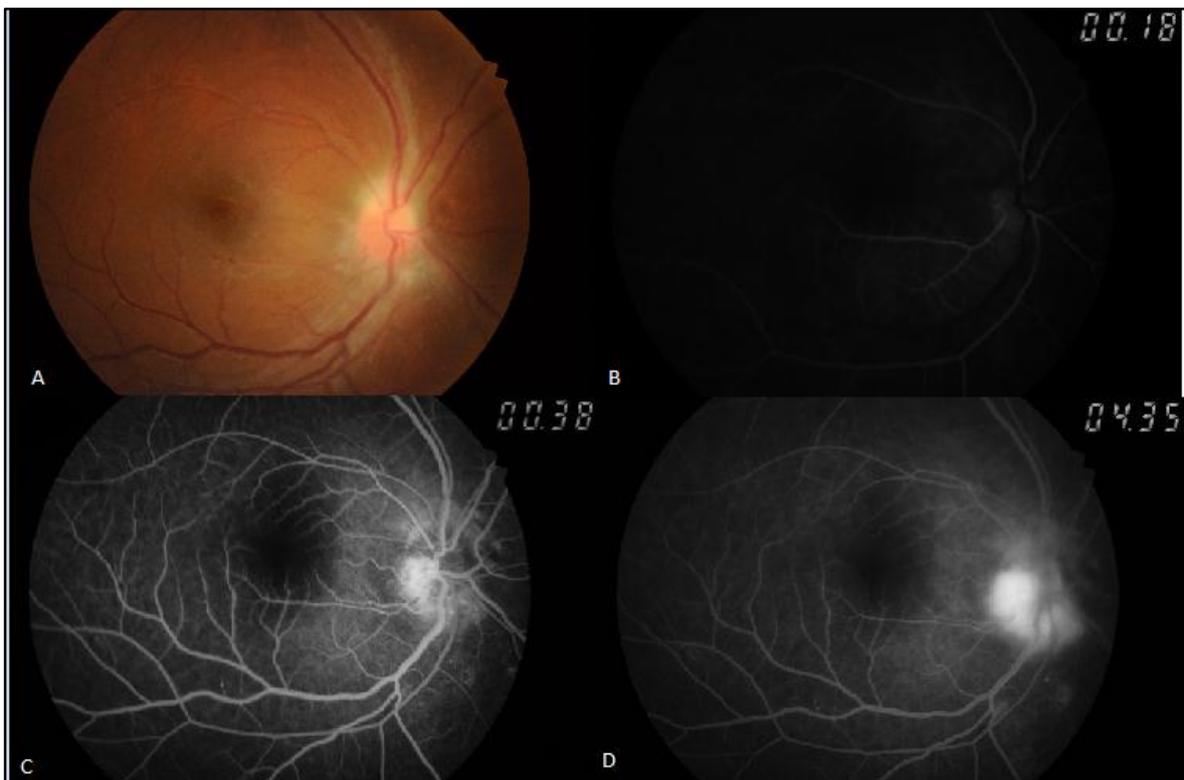
Ocular Finding	Number of Patients
Posterior Segment Manifestation	
Type 1 Takayasu retinopathy	10
Type 2 Takayasu retinopathy	4
Type 3 Takayasu retinopathy	22
Ocular ischaemic Syndrome	2
Retinal Vasculitis	8



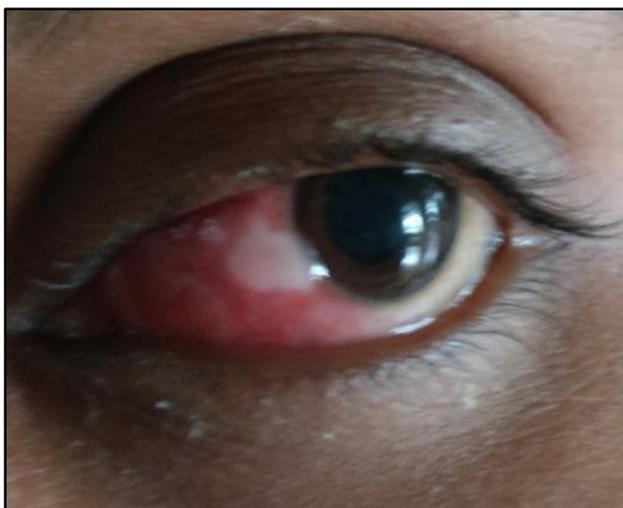
**Image 1. A. Fundus of right eye revealing a clear media with pre retinal haemorrhages around the disc and in the inferior retina. B. Fundus of the left eye showing arteriolar attenuation with AV crossing changes with few cotton wool spots. C. Posterior subcapsular cataract seen in the right eye in retro illumination D. Fundus of the right eye with complete resolution of haemorrhages. Haziness of the media is due to the development of cataract**



**Image 2. A. Normal filling of the disc and vessels with intact foveal avascular zone. B. Vascular staining and capillary non perfusion areas seen in the superotemporal quadrant**



**Image 3. A. Fundus of right eye with inferior segmental disc edema. B,C,D. Phases of fundus fluorescein angiography showing differential filling pattern of the disc and normal filling of the vessels.**



**Image 4. Acute Scleritis in a Patient with Takayasu Arteritis**

**DISCUSSION**

Takayasu arteritis is a chronic inflammatory arteritis affecting large vessels, predominantly the aorta and its main branches characterised by inflammation of the vessel wall leading to wall thickening, fibrosis, stenosis, and thrombus formation. It is also known as pulseless disease, occlusive thromboaropathy and Martorells syndrome. Acute inflammation can destroy the arterial media and lead to aneurysm formation. Early reports suggested that the disease was confined to females from Eastern Asia, but it has now been recognised worldwide in both sexes, although disease manifestations vary between populations.<sup>4</sup> Depending upon the site and extent of the vasculature involved as determined by Magnetic resonance Angiography, Takayasu arteritis can be classified in to five types (Table 3).<sup>5</sup>

Type of Takayasu Arteritis	Vasculature Involved
Type I	Aortic arch and its branches
Type II	a. ascending aorta, aortic arch and its branches b. thoracic descending aorta is involved in addition to type IIA
Type III	Thoracic descending aorta, abdominal aorta and/ or renal arteries
Type IV	Abdominal aorta or renal aorta
Type V	Entire aorta with its branches

**Table 3**

The exact pathogenesis of the arteritis is still unknown. Tuberculosis, streptococcal infections, rheumatoid arthritis and other collagen vascular diseases had been debated for its aetiology in the past, recently more emphasis has been given on immunopathological cause. Recent studies strongly suggest association of interleukin-6 and RANTES (regulated on activation, normal T cell expressed and secreted) in the pathogenesis of the disease process. Histopathology of the involved vessels suggests that the initial site of inflammation is around the vasa vasorum which are small arteries in the media and adventitia.<sup>6</sup>

The exact incidence of ocular involvement in cases with Takayasu arteritis has not yet been defined. In our study 82.5% of the patients were females as shown by Hall et al<sup>1</sup> The occlusive arteritis of the aortic arch branches results in ischemic manifestations which are termed as Takayasu retinopathy whilst the involvement of the renal artery or suprarenal aorta causes retinal changes due to severe and uncontrolled hypertension.<sup>7</sup>

There have been reports of anterior ischemic optic neuropathy,<sup>8,9</sup> and retinal artery occlusion,<sup>10,11</sup> occurring in conjunction with Takayasu arteritis. Many other vision threatening manifestations like ocular ischemic syndrome, keratitis,<sup>12</sup> and scleritis,<sup>13</sup> have also been reported in association with Takayasu arteritis. Even coats disease,<sup>14</sup> like phenomenon has been described in patients with Takayasu arteritis. We have seen a large number of patients with various eye findings in Takayasu arteritis in the study period. This is because our centre is a tertiary eye care referral institute.

The ischemic retinal changes in Takayasu arteritis depend on which portion of the carotid arteries become occluded and the rate of development and duration of ocular vascular insufficiency and the effectiveness of collateral blood supply to the eye. Occlusion of the aortic arch and its branches resulted in anterior ischemic optic neuropathy and direct involvement of the central retinal artery has resulted in central retinal artery occlusion in our patients with hypoperfusive manifestations. The involvement of the abdominal and renal arteries leads to uncontrolled hypertension and hypertensive manifestation in the other patient. Therefore in our study major hypoperfusive ocular manifestation were seen in patients with mainly type 1 and

type 2 Takayasu arteritis. Similar findings were observed by Peter J et al in their study.<sup>15</sup>

Management of Takayasu arteritis is difficult because of the difficulty in early diagnosis before critical stenosis or occlusion and lack of uniform parameters for grading the disease activity. The most commonly used therapeutic agents include Corticosteroids and conventional immunosuppressive agents, such as Methotrexate and mycophenolate mofetil. In patients who remain resistant and/or intolerant to these agents, biologics, including anti-TNF agents, infliximab and tocilizumab, seem promising. Antiplatelet treatment may lower the frequency of ischaemic events in these patients. In the presence of a critical short-segment arterial stenosis, the principle of treatment is mainly revascularization of the affected organs by endovascular interventions including balloon angioplasty or stent graft replacements. On the other hand, long-segment stenosis with extensive periarterial fibrosis or occlusion requires surgical bypass of the affected segment, which is clearly associated with superior results compared with endovascular intervention.<sup>16</sup> Control of the systemic factors leads to delay in the development of the chronic hypertensive manifestations. Ischaemic manifestations like arterial occlusions or ischaemic optic neuropathy might not show drastic improvement with stenting and other methods of revascularisation. And may not result in significant improvement in visual acuity due to irreversible ischaemic damage to the optic nerve.

**CONCLUSION**

This study is to highlight the fact that Takayasu arteritis can present with multitudinous ocular manifestations which can be hypertensive or hypoperfusive and can lead to significant ocular morbidity if not for timely intervention. It can result in irreversible damage to the retina and optic nerve due to perfusional abnormalities. Since majority of patients are young the consequences of these sight threatening manifestations are devastating. Though manifestations like anterior ischaemic optic neuropathy and central retinal artery occlusion may not be amenable to therapy, chronic hypertensive manifestations can be controlled by adequate medical therapy. This study is to strongly emphasise routine and regular ophthalmic screening in patients with Takayasu arteritis at the time of diagnosis and also at adequate intervals to diagnose significant treatment related complications like steroid induced cataract at an early stage.

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