

## Giant cell arteritis: Its ophthalmic manifestations

Sohan Singh Hayreh

Giant cell arteritis (GCA) is the most important medical emergency in ophthalmology, because its most dreaded complication is visual loss, which is preventable if these patients are diagnosed early and treated immediately and aggressively. This is a brief review of GCA, its ophthalmic manifestations, and how to diagnose and manage them.

**Key words:** Anterior ischemic optic neuropathy, Central retinal artery, Giant cell arteritis, posterior ciliary artery occlusion

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Giant cell arteritis (GCA) is the most important medical emergency in ophthalmology, because its most dreaded complication is visual loss. Kearns<sup>[1]</sup> rightly stressed that GCA “ranks as the prime medical emergency in ophthalmology, there being no other disease in which the prevention of blindness depends so much on prompt recognition and early treatment.” But, *blindness in GCA is preventable if these patients are diagnosed early and treated immediately and aggressively.*

## Giant Cell Arteritis

GCA is an immune-mediated, systemic granulomatous vasculitis, affecting medium and large arteries, which have the internal elastic lamina. I have investigated GCA and its ophthalmic manifestations since 1965. I have discussed at length various aspects of GCA elsewhere.<sup>[2]</sup> Following is a brief up-dated account.

In 1890 Jonathan Hutchinson<sup>[3]</sup> first reported the case of an English man who had pain on wearing a hat because of pain in his temples, and he called it “thrombotic arteritis”. This disease was later described by Schmidt<sup>[4]</sup> in 1930. Horton *et al.*<sup>[5]</sup> in 1932 described it as “temporal arteritis”. It was not till 1941 that the correct pathological term, “GCA” was used.<sup>[6]</sup>

## Racial differences

GCA is far more common among Caucasians than other races; however, it is reported among non-Caucasians all over the world, e.g., from China<sup>[7-10]</sup>, Taiwan<sup>[11]</sup>, Korea<sup>[12]</sup>, Japan<sup>[13]</sup>, Thailand<sup>[14,15]</sup>, Malaysia<sup>[16]</sup>, Israel<sup>[17]</sup>, Arabs<sup>[18]</sup>, Mexicans<sup>[19]</sup>, African American<sup>[20,21]</sup>, and Alaskan Natives.<sup>[22]</sup> There are several reports of variable numbers of patients of GCA from India, including from the Punjab<sup>[23-26]</sup>, New Delhi<sup>[27]</sup>, Mumbai<sup>[28]</sup>, Goa<sup>[29]</sup>,

South India<sup>[30-35]</sup>, and Assam.<sup>[36]</sup> I am from Punjab originally, and I developed GCA in 2011, and two of my siblings also developed it at other times. It seems GCA is underdiagnosed in India. This may be because of the prevalent impression among Indian physicians that GCA does not exist in India.

## Demographic characteristics

In our prospective study of 170 patients with GCA, the age range was 56 to 93.4 years.<sup>[20]</sup> Several studies have shown that the incidence of GCA increases with age. Our study showed that women developed GCA 3 times more often than the men. Women are far more susceptible to autoimmune diseases; why women have stronger immune responses is not clear. A stew of biological factors may be responsible, including the hormone estrogen which appears to play a role in immunity, and the fact that women have two X chromosomes, which contain immune-related genes. Our study about seasonal variations for onset of GCA showed no significant seasonal differences.<sup>[2]</sup>

## Systemic symptoms and signs of GCA

There is a large amount of contradictory data available on the signs and symptoms of GCA. Pauley and Hughes<sup>[37]</sup> in 1960 stated that “when elderly people begin to fail mentally and physically, this disorder should be one of the first to be considered”. In the literature it is mentioned that GCA patients may complain of one or more of the following symptoms: headache, scalp tenderness, neck pain, malaise, myalgia, anorexia, weight loss, anemia, jaw claudication, polymyalgia rheumatica symptoms, abnormal temporal arteries, flu-like symptoms, fever of unknown etiology and other vague systemic symptoms. Other ischemic lesions which can develop in GCA

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include ischemic stroke, coronary arteritis, and myocardial infarction, mesenteric involvement, and scalp necrosis.

To ascertain the validity, reliability, sensitivity, and specificity of various signs and symptoms of and diagnostic tests for early diagnosis of GCA, we studied 363 patients who had temporal artery biopsy (TAB) for suspected GCA.<sup>[38]</sup> Of those, TAB was positive in 106 and negative in 257. The odds of a positive biopsy were 9.0 times greater with jaw claudication ( $P < 0.0001$ ), 3.4 times greater with neck pain ( $P = 0.0085$ ), 2.0 times greater with an erythrocyte sedimentation rate (ESR) of 47 to 107 mm/hour ( $P = 0.0454$ ), 3.2 times greater with C-reactive protein (CRP) above 2.45 mg/dl ( $P = 0.0208$ ), and 2.0 times greater for age 75 years or more ( $P = 0.0105$ ). Incidence of anorexia/weight loss ( $P = 0.0005$ ) and fever ( $P = 0.040$ ) was statistically higher in those with positive than negative TAB. In the literature, headache is stressed as the most characteristic symptom of GCA, but in our study its incidence between TAB positive versus negative was not statistically significant ( $P = 0.084$ ). This may be because headache is common in the general population and some had TAB because of headache. Similarly, the incidents of malaise ( $P = 0.177$ ), myalgia ( $P = 0.606$ ), abnormal temporal artery ( $P = 0.105$ ), scalp tenderness ( $P = 0.058$ ) and anemia ( $P = 0.730$ ) were not significantly different between positive and negative TAB patients. When I was diagnosed with GCA, at the onset I had unexplained fever and no other systemic symptoms; my ESR  $> 140$  mm/hr and CRP 17.1 mg, - both very high, and I had a positive TAB.

Recently it was postulated that GCA vasculitis is driven by deposition of herpes zoster antigen in the temporal artery.<sup>[39]</sup> However, a more recent study<sup>[40]</sup> was not able to document herpes zoster antigen positivity in the TAB biopsies from GCA patients.

### Occult GCA

*It is widely believed by physicians and ophthalmologists that GCA patients always present with systemic symptoms and high ESR, and that their absence rules out GCA. This impression has, sadly, caused misdiagnosis and consequent blindness, because both may sometimes be absent* (see below). In 1962 Simmons and Cogan<sup>[41]</sup> described occult GCA, which is now a well-established clinical entity. These patients have no systemic symptoms of GCA in spite of having a positive TAB for GCA; but all have elevated ESR and CRP.

We<sup>[42]</sup> investigated the incidence of occult GCA in a prospective study of TAB confirmed GCA patients, who had no systemic symptoms or signs of GCA whatsoever, and all had ocular involvement. In that study, 21.2% fulfilled all the criteria for occult GCA, i.e., they had TAB confirmed GCA and the majority had elevated ESR and CRP, and/or arteritic anterior ischemic optic neuropathy (A-AION). CRP is far more reliable than ESR because we have seen ESR of 4-5 mm/hr in patients with positive TAB for GCA. Because they have no systemic symptoms, such patients do not go to rheumatologists and would not be included in rheumatologic studies. Since occult GCA is a potential cause of blindness, 21.2% is an unacceptably high number to be missed. Therefore, *the absence of systemic symptoms and normal ESR do not rule out GCA—an extremely important point to be borne in mind to prevent blindness.*

### Clinical criteria used to diagnose GCA

Since the most dreaded complication of GCA is visual loss, the key to preventing that is *to establish diagnosis early, and to institute therapy immediately.* Various criteria for diagnosis of GCA are discussed at length elsewhere.<sup>[2]</sup>

Almost invariably, patients suspected of GCA are referred to rheumatologists. The following five criteria advocated by the American College of Rheumatologists (ACR)<sup>[43]</sup> are generally

accepted as the “gold standard” by rheumatologists for diagnosis of GCA: (1) age  $\geq 50$  years at onset, (2) new onset of localized headache, (3) temporal artery tenderness or decreased temporal artery pulse, (4) elevated ESR—Westergren  $\geq 50$  mm/h, and (5) positive TAB for GCA. They stated that: “A patient shall be classified as having GCA if at least three of these five criteria are met.” But in the ACR study, 8.4% patients’ TAB was either negative for GCA or not done, and that study advocated that in such cases new headache and scalp tenderness or nodules be “used as a surrogate”.

As discussed above, our study<sup>[38]</sup> showed on logistic regression analysis that the odds of having TAB-positive GCA were 9.0 times greater with jaw claudication, 3.4 times with neck pain, and 3.2 times with CRP above 2.45 mg/dl than those without them. Elevated CRP was found to be the most reliable test. Elevated ESR is suggestive of GCA but *it is important to remember that normal ESR does not rule out GCA*; we have seen ESR of 4-5 mm/hr in patients with positive TAB for GCA. The ACR study’s five criteria do not include these important measures, which are very helpful in diagnosis of GCA to prevent visual loss. Also, our study showed that headache and scalp tenderness are unreliable criteria. Thrombocytosis was seen in 57% of those with TAB positive for GCA.<sup>[44]</sup> Our study<sup>[42]</sup> showed that 21% of GCA patients had occult GCA. Thus the current ACR criteria for diagnosis of GCA are not reliable to prevent blindness and should not be used for diagnose GCA.

The most useful information comes from a combination of systemic symptoms and signs, ESR and CRP. Occlusion of the posterior ciliary artery (PCA) is a hallmark of GCA. My studies have shown that fluorescein fundus angiography provides the most critical information about the evidence of PCA occlusion (see below).

In a GCA, where a patient is in imminent danger of developing blindness, neuroradiological and Doppler tests, with false negative results, are not only *not* highly reliable, but also not cost-effective when compared with the above readily available, cheap and highly reliable tests. They are not indicated in routine clinical practice.

### Temporal Artery Biopsy (TAB)

TAB is considered as the “gold standard” criterion for diagnosis of GCA. However, false-negative biopsies have been reported, attributed to “skip areas” of arteritis. We recommend: (a) since GCA is a well-known masquerader, TAB should be done in every patient suspected of having GCA, even if the diagnosis is evident from other findings discussed above; (b) at least a one-inch piece of the temporal artery should be obtained, and (c) serial sectioning of the biopsy is critical to get valid information—in one of the biopsies in our study, only one of about 300 serial sections of the biopsy showed definite evidence of GCA. Most evidence indicates that corticosteroid therapy does not alter the TAB results. *If there is a high index of suspicion of GCA, it is not advisable to wait for TAB results to initiate corticosteroid therapy, because by the time biopsy results are available, the patient may have suffered irreversible visual loss.*

### Ophthalmic Manifestations of GCA

Visual loss in one or both eyes as an ocular complication in GCA was first reported in 1937 by Horton and Magath<sup>[45]</sup> and in 1938 by Jennings.<sup>[46]</sup> Since then, an enormous literature has accumulated on the subject. *Visual loss is now well established as the most dreaded and irreversible complication of GCA, that makes GCA an ophthalmic emergency.*

Among the orbital arteries, GCA has a special predilection for the PCAs, which supply the choroid, optic nerve head

and cilioretinal artery. The ocular lesions seen in GCA are primarily ischemic in nature, invariably due to thrombosis by granulomatous inflammation of one or more of the PCAs, and rarely of the ophthalmic artery; occlusion of the PCAs has been demonstrated by fluorescein fundus angiographic<sup>[20,47,48]</sup> [Fig. 1] and by many histopathological<sup>[2]</sup> [Fig. 2] studies.

### Incidence of ocular involvement in GCA

The reported incidence of ocular involvement varies widely, from 20% to 70%. Two Swedish, mostly Caucasian population-based studies, reported visual complications in 10%<sup>[49]</sup> and 13.4%<sup>[50]</sup> after the onset of GCA. It has been reported that the risk of permanent visual loss secondary to GCA increases with age but is lower in patients presenting with constitutional symptoms.<sup>[51]</sup>

We conducted a systematic, prospective study of the ocular manifestations of GCA, using the strict criterion of positive TAB for GCA diagnosis.<sup>[20]</sup> There were 170 consecutive patients with TAB proven GCA, from our region, which is predominantly Caucasian. In that series, the incidence of ocular involvement was 50% and that of visual loss 49%. We feel that this may reflect a more realistic incidence, because every patient had the strict criterion of positive TAB of GCA and patients were referred for TAB biopsy to our department by all physicians in our large multispecialty university hospital. In the 85 patients with ocular involvement, the ocular symptoms were of varying severity - diplopia in 6% and eye pain in 8%, and ocular ischemic lesions consisted of amaurosis fugax in 31%, A-AION in 81%, cilioretinal artery occlusion in 22%, central retinal artery occlusion (CRAO) in 14%, and arteritic posterior ischemic optic neuropathy (A-PION) in 7%.

Bilateral visual loss in GCA has been reported in the literature at widely differing rates. In our series, this was seen at the initial visit in 32%. Of those patients, 17% became aware of the visual loss in both eyes at the same time, whereas in the rest, the time interval between the visual losses in the two eyes varied from one day to more than 6 months. In all our patients who complained of simultaneous loss of vision in both eyes, fundus examination revealed that in fact one eye had older changes than the newly involved eye; this indicates that these patients were not aware of visual loss in the first eye until the second eye was involved, giving an erroneous impression of simultaneous visual loss in both eyes. Thus, *the incidence of initial ocular involvement as well as involvement of the second eye in GCA, very much depends upon when the diagnosis is made, how early the patient is seen, and how aggressively systemic corticosteroid therapy is used.*

### Classification of ophthalmic ischemic lesions of GCA

These may be classified according to various anatomical parts of the eye involved.

**Optic nerve:** Amaurosis fugax, A-AION, A-PION.

**Retina:** CRAO, cilioretinal artery occlusion, cotton-wool spots.

**Choroid:** Choroidal ischemic lesions.

**Anterior segment:** Anterior segment ischemia, pupillary abnormalities.

**Extraocular muscle:** Extraocular muscle ischemia and motility disorders.

**Ocular ischemic syndrome**

**Orbital:** Orbital inflammatory syndrome.

**Cerebral ischemic lesions:** That produces visual loss.

I have investigated ophthalmic ischemic lesions of GCA since 1969. All these lesions are discussed at length elsewhere<sup>[2,20]</sup>; following is an abbreviated account.

### Amaurosis fugax

Amaurosis fugax is a well-recognized complication of GCA. In our study<sup>[20]</sup> it was reported by 31% of those with ocular involvement. It preceded the development of permanent visual loss - in 39% of the A-AION, 15% of the CRAO, 3% of the A-PION and 6% of those with A-AION combined with cilioretinal artery occlusion. The findings indicate that *amaurosis fugax is an important early visual symptom of GCA and an ominous sign of impending blindness.*

### Ischemic optic neuropathies

These consist of A-AION and A-PION.

#### Arteritic AION

This is by far the most common and devastating ocular complication of GCA, resulting in sudden, permanent, partial or complete visual loss, involving one or both eyes. In our series<sup>[20]</sup>, it was seen in 76%. Since PCA circulation is the main source of blood supply to the optic nerve head, occlusion of the PCA results in infarction of a segment or the entire optic nerve head [Fig. 2], and the occlusion can be demonstrated on fluorescein fundus angiography [Fig. 1] and histopathology [Fig. 2]. On ophthalmoscopy, the presence of chalky white optic disc edema [Figs. 1, 3, 4] and on fluorescein angiography evidence of PCA occlusion [Fig. 1] are almost diagnostic of A-AION (seen in 69%<sup>[20]</sup>). The optic disc edema resolves within 6–8 weeks, and the disc becomes atrophic and usually develops cupping [Fig. 4c] indistinguishable from that seen in glaucomatous optic neuropathy. When a cilioretinal artery is present, it is also occluded along with A-AION [Fig. 1]. Thus, *3 diagnostic features of GCA are: (a) chalky white optic disc edema, (b) PCA occlusion, and (c) A-AION combined with cilioretinal artery occlusion. A-AION is an ophthalmic emergency; these patients require immediate and aggressive treatment with high-dose systemic corticosteroids to prevent further visual loss.*

The differential diagnosis of A-AION from non-arteritic AION is discussed at length elsewhere.<sup>[48]</sup>

#### Arteritic PION

This is due to occlusion by GCA of orbital arteries, which supply small nutrient arteries to the posterior part of the optic nerve. Its clinical features, pathogenesis, and management are discussed at length elsewhere.<sup>[52]</sup> During the acute phase, optic disc and fluorescein angiography are normal, but usually in 6–8 weeks the disc develops pallor.

### Central retinal artery occlusion

In our series<sup>[20]</sup> this was seen in 12% of the eyes of the GCA patients. CRAO is almost invariably combined with PCA occlusion—the latter detected only on fluorescein fundus angiography<sup>[47]</sup> [Fig. 5]. This is because the central retinal artery arises from the ophthalmic artery, almost always by a common trunk with one or the other PCA [Fig. 6]. CRAO has a classical ophthalmoscopic appearance.<sup>[53]</sup> *As a rule, when persons 50 years or older present with CRAO, fluorescein fundus angiography must be performed to find out if there is underlying PCA occlusion as well, because its presence is virtually diagnostic of CRAO due to GCA.* Such patients require immediate and aggressive corticosteroid therapy to prevent catastrophic visual loss.

### Cilioretinal artery occlusion

The cilioretinal artery arises directly or indirectly from the PCA. Since GCA has a special predilection for involving the PCAs, it is not surprising to see *simultaneous development of both A-AION and cilioretinal artery occlusion*, when an eye has a cilioretinal artery. These eyes present a classical, diagnostic clinical picture of GCA, i.e., *a combination of chalky white optic disc edema, retinal infarct in the region of the occluded cilioretinal artery and PCA occlusion on fluorescein angiography* [Fig. 1]. Thus, *as a*

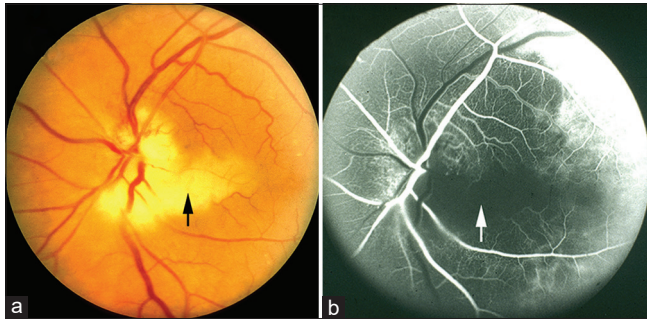
rule, in all patients 50 years and older, it is essential to rule out GCA in all patients with cilioretinal artery occlusion (erroneously called "branch retinal artery occlusion") to prevent catastrophic visual loss.

### Cotton-wool spots

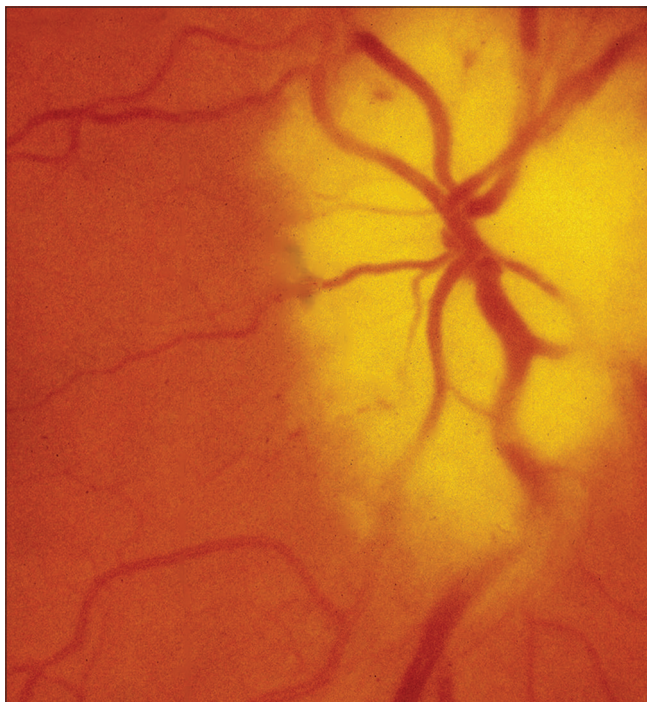
One third of the eyes with visual loss in our series<sup>[20]</sup> had retinal cotton-wool spots at the posterior pole during early stages of the disease [Fig. 7]. They represent focal inner retinal ischemic lesions. In GCA, these are most probably due to platelet microembolization from the partially thrombosed regional arteries.

### Choroidal ischemic lesions

In GCA, occlusion of the PCAs may, in addition to A-AION, produce patches of choroidal infarcts, which after 2–3 weeks



**Figure 1:** Left eye with A-AION and cilioretinal artery occlusion. (a) Fundus photograph showing chalky-white optic disc edema and a patch of retinal opacity in the distribution of the cilioretinal artery occlusion. (b) Fluorescein angiogram showing normal filling of the central retinal artery and of the choroid supplied by the lateral PCA, but no filling of the choroid and optic disc supplied by the medial PCA as well as of the cilioretinal artery (arrow). Note the supply by the medial PCA extends all the way up to the fovea involving the entire optic disc



**Figure 3:** Fundus photograph of right eye with A-AION showing characteristic chalky-white optic disc edema with two small superficial retinal hemorrhages in upper part

appear as peripheral chorioretinal degenerative lesions [Fig. 8]. They are usually located in the mid-peripheral region of the fundus and frequently are triangular in shape with their base towards the equator and apex towards the posterior pole.

### Anterior segment ischemia

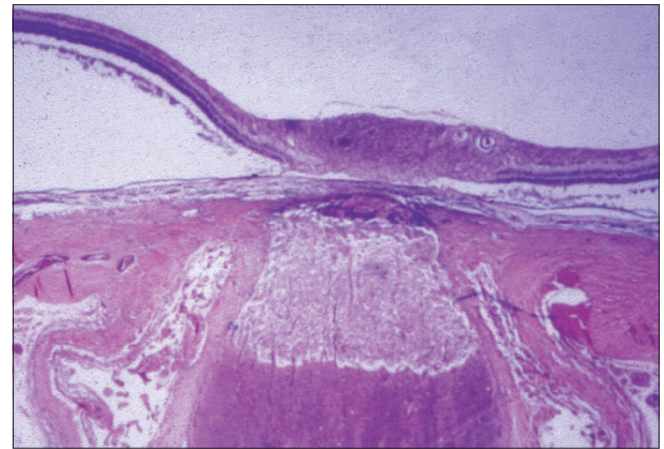
This is a rare complication of GCA. Ocular hypotony, corneal edema, iris ischemia, pupillary abnormality and marked visual loss are its manifestations. It may be erroneously diagnosed as anterior uveitis.

### Pupillary abnormality

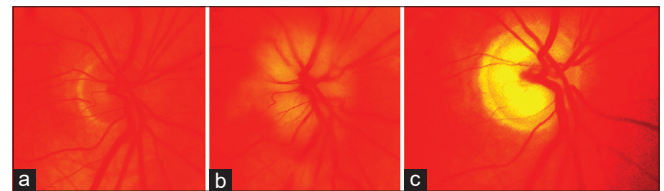
This is seen in association with visual loss and iris ischemia produced by GCA.

### Extra-ocular motility disorders

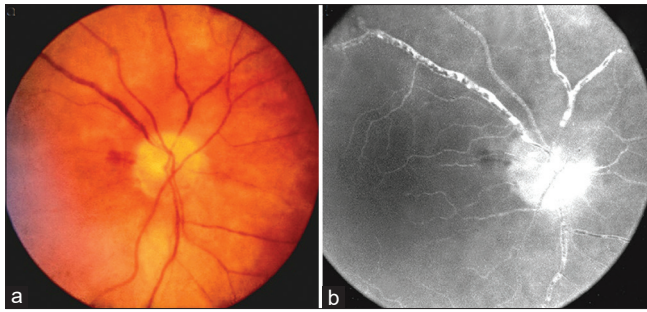
There are many anecdotal case reports of development of diplopia in GCA due to involvement of the extraocular muscle, with or without visual disturbance. In our series<sup>[20]</sup> of 170 GCA patients, the incidence was 6% and it was only transient in all; however, this may be an underestimate because if one eye is blind or has severe visual loss, no diplopia may be experienced in spite of extraocular muscle palsy. There are two theories about the cause of ocular motility disorders in GCA: neurogenic and myogenic. According to the neurogenic theory, these disorders are attributed to ischemia of one or more of the three oculomotor nerves, or possible to brain-stem ischemia. That seems unlikely because the various oculomotor nerves are supplied by fine nutrient vessels which cannot be selectively involved by GCA - in GCA only medium-sized and large arteries are involved. The



**Figure 2:** Photomicrograph of the optic nerve head (ONH) and retrolaminar optic nerve of right eye with 4-week-old A-AION showing a well-defined area of infarction of the ONH and retrolaminar region (Verhoeff's modified elastic stain) (Reproduced from MacMichael and Cullen. In: Proceedings, 2<sup>nd</sup> William Mackenzie Symposium on the optic nerve. London: Kimpton; 1972. p. 108–116.)



**Figure 4:** Fundus photographs of right eye (a–c) of a patient with GCA with A-AION and no light perception. (a) Normal right eye 5 days before developing A-AION. (b) Right eye one day after development of A-AION. (c) Right eye 4 months after developing A-AION shows resolution of optic disc edema and development of optic disc cupping



**Figure 5:** Right eye with combined A-AION and CRAO. (a) Fundus photograph shows pallor with mild disc edema in lower part and box-carring (cattle-trucking) in the retinal vessels. (b) Fluorescein angiogram during the late phase showing boxcarring in the retinal vessels, with disc staining in the lower half and no filling of the choroid because of PCA occlusion

myogenic view seems more plausible, representing ischemic myopathy of one or more of the extraocular muscles, as a result of arteritic occlusion of one or more of the arteries supplying the extraocular muscles. In patients over the age of 50 years, with a recent history of diplopia, it is essential to rule out GCA.

**Orbital complications**

Proptosis with pseudotumor or alone has occasionally been reported in GCA. Orbital infarction with ischemia of all orbital structures, orbital apex syndrome or periorbital ecchymosis have also been reported.

**Cerebral ischemic lesions producing visual loss**

GCA is also called “cranial arteritis”. Therefore, cerebral ischemic lesions can produce visual loss; however, this is extremely rare. Rarely, occipital lobe infarct results in homonymous hemianopia. I have had only one such case among about 300 GCA patients seen in my clinic. This may be an underestimate because they primarily consult neurologists.

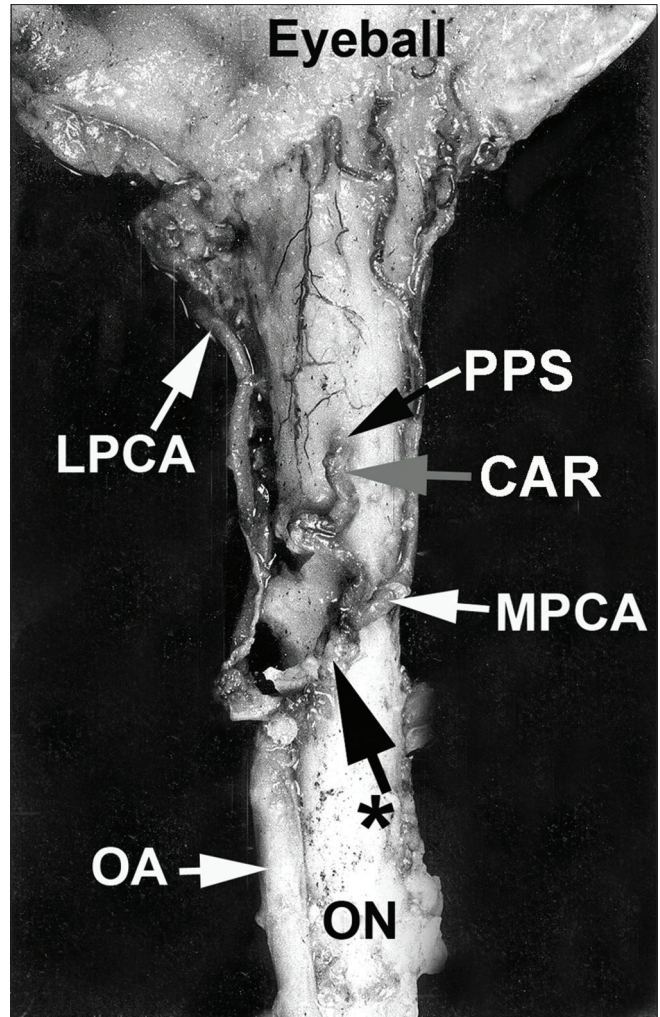
**Management of GCA**

This is highly controversial. As mentioned above, GCA patients are usually referred to rheumatologists for management; but rheumatologists and ophthalmologists have different perspectives on GCA.<sup>[54]</sup> Rheumatologists deal with patients essentially with rheumatologic manifestations of GCA, while ophthalmologists see GCA patients with visual loss or patients with occult GCA<sup>[42]</sup> who lose vision without having any rheumatologic or other systemic symptoms. Therefore, for ophthalmologists GCA is a blinding disease with tragic consequences, whereas for rheumatologists it is a disease mainly with rheumatologic complaints, not very serious. Moreover, rheumatologists consider GCA and polymyalgia rheumatica (PMR) as one disease entity and recommend a treatment regimen which may be appropriate for PMR (which carries no risk of blindness), but falls well short of the therapy required to prevent blindness in GCA patients.

Management of GCA is discussed at length elsewhere.<sup>[2,54]</sup> *To prevent blindness in GCA, early and adequate treatment of GCA is key.* Following is an abridged account.

**Corticosteroid therapy**

This remains the key treatment of GCA to prevent the occurrence or progression of visual loss. Therefore, it is important to discuss it in detail. The mode (intravenous or oral) and dosage of corticosteroid therapy in GCA are a highly controversial.



**Figure 6:** Example of a common trunk of origin of central retinal artery and PCA from the ophthalmic artery as seen from below—central retinal artery and medial PCA arising by a common trunk. CRA = Central retinal artery; LPCA = Lateral PCA; MPCA = Medial PCA; OA = Ophthalmic artery; ON = Optic nerve; \* Common trunk of origin of CRA and PCA

Following comments are based on our study<sup>[54]</sup> and on my management of over 300 GCA patients with and without visual loss for more than 50 years. I divide corticosteroid therapy in GCA into three distinct phases, to prevent visual loss:

1. Regimen of treatment during the initial acute phase.
2. Regimen during the tapering phase.
3. Maintenance dose.

**Treatment during the initial acute phase**

It is controversial whether to prescribe high-dose intravenous or just oral corticosteroids for treatment of acute visual loss in GCA. I have discussed that elsewhere.<sup>[55]</sup>

**Intravenous corticosteroid therapy**

Based on my experience, my recommendation is to give initially one intravenous mega dose (equivalent to 1,000 mg of Prednisone) followed by high-dose (80–120 mg) oral Prednisone to patients who present with: (1) history of amaurosis fugax, (2) complete or marked loss of vision in one eye or (3) early signs of involvement of the second eye. These patients have a high risk of further visual loss, and one must try to achieve a high blood concentration of corticosteroids immediately, which is not



**Figure 7:** Fundus photograph of left eye of a patient with GCA with two cotton-wool spots

possible with oral therapy. My overall strategy is: the greater the visual loss or potential for visual loss, the more aggressive the corticosteroid therapy, to prevent any further visual loss. After that, all patients are switched on to high-dose oral Prednisone.

#### Oral corticosteroid therapy

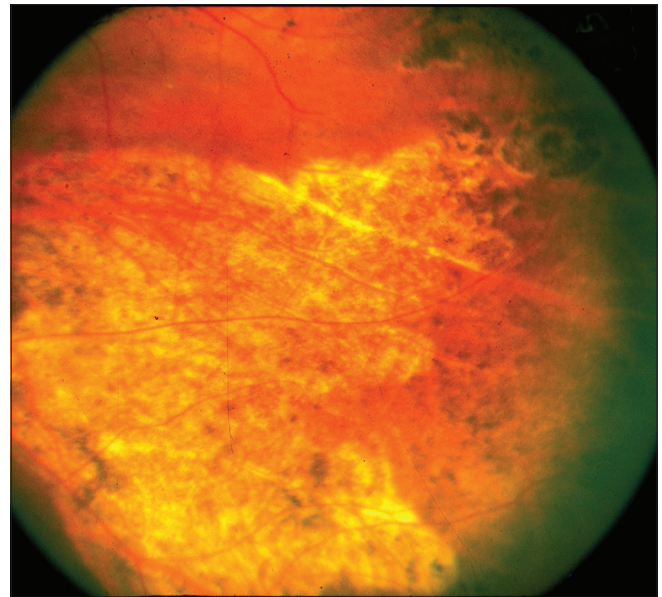
This is to start with 80 mg/day of Prednisone. Some have advocated giving 1 mg/kg prednisone.

#### Monitoring GCA response to the corticosteroid therapy

Based on my experience and our study,<sup>[54]</sup> the only reliable method to regulate and monitor this therapy is by doing ESR and CRP repeatedly. After the start of high-dose corticosteroid therapy, both ESR and CRP are repeated every 2–3 days while the patient is on the high dose. As shown in Fig. 9, both ESR and CRP progressively come down till they reach a stable level. ESR takes longer than the CRP to reach a stable level. The lowest levels of ESR and CRP achieved by this method actually represent the baseline ESR and CRP for that individual, which shows interindividual variation. That level then acts as the benchmark to maintain while subsequently tapering the therapy. I have found that to be the only satisfactory means to monitor corticosteroid therapy to prevent visual loss. The tapering down of corticosteroid therapy should not be started until both the ESR and CRP have reached their lowest and stable levels.

#### For tapering down corticosteroid therapy and to determine the maintenance dose of therapy

After ESR and CRP have reached their lowest, stable levels, Prednisone dosage is slowly decreased. *The guiding principal in monitoring and tapering down the corticosteroid therapy and finding the maintenance dose is to achieve the lowest levels of ESR and CRP with the lowest possible dose of Prednisone.* There is a marked interindividual variation among GCA patients in the required tapering regimen, maintenance dose required and the time it takes to reach that goal. Therefore, *no generalization at all is possible regarding tapering down the Prednisone; it has to be individualized; likewise, there is no set formula or any other way to predict the maintenance dose required by a particular patient.* This is in sharp contrast to the views of rheumatologists, who generally recommend *systemic symptoms* as their guide in tapering down of the therapy and its duration. However, to prevent development of visual loss or its further deterioration during follow-up, I have found systemic symptoms are totally unreliable, because (a) I have seen patients going blind because



**Figure 8:** Fundus photograph of left eye of a patient with GCA and A-IION several months after visual loss showing a magnified view of the peripheral chorioretinal lesions. The eye also had optic atrophy

of that, and (b) I have so often found rise in levels of ESR and CRP (with risk of visual loss) without recurrence of symptoms.<sup>[56]</sup> Tapering down Prednisone in GCA is certainly laborious and time-consuming. But in my study, where the patients have been followed for many years or even decades on the above regimen of treatment, *not a single patient suffered any further visual loss after the first 5 days from the start of high dose corticosteroid therapy.*<sup>[57]</sup> This shows that, for monitoring corticosteroid therapy in GCA, *a titration of the corticosteroid dosage with the levels of ESR and CRP is the only safe and reliable method.*

#### Maintenance dose of prednisone

In GCA, as in most other rheumatological diseases, the corticosteroid therapy is suppressive and not curative; the vast majorities of patients require a highly variable, carefully adjusted maintenance dose for many years and perhaps lifelong, to prevent visual loss and relapses. The maintenance dose required to keep GCA under control in my studies usually varied from 1 to 5 mg daily, without any systemic side-effects.

#### My personal experience of GCA and corticosteroid therapy

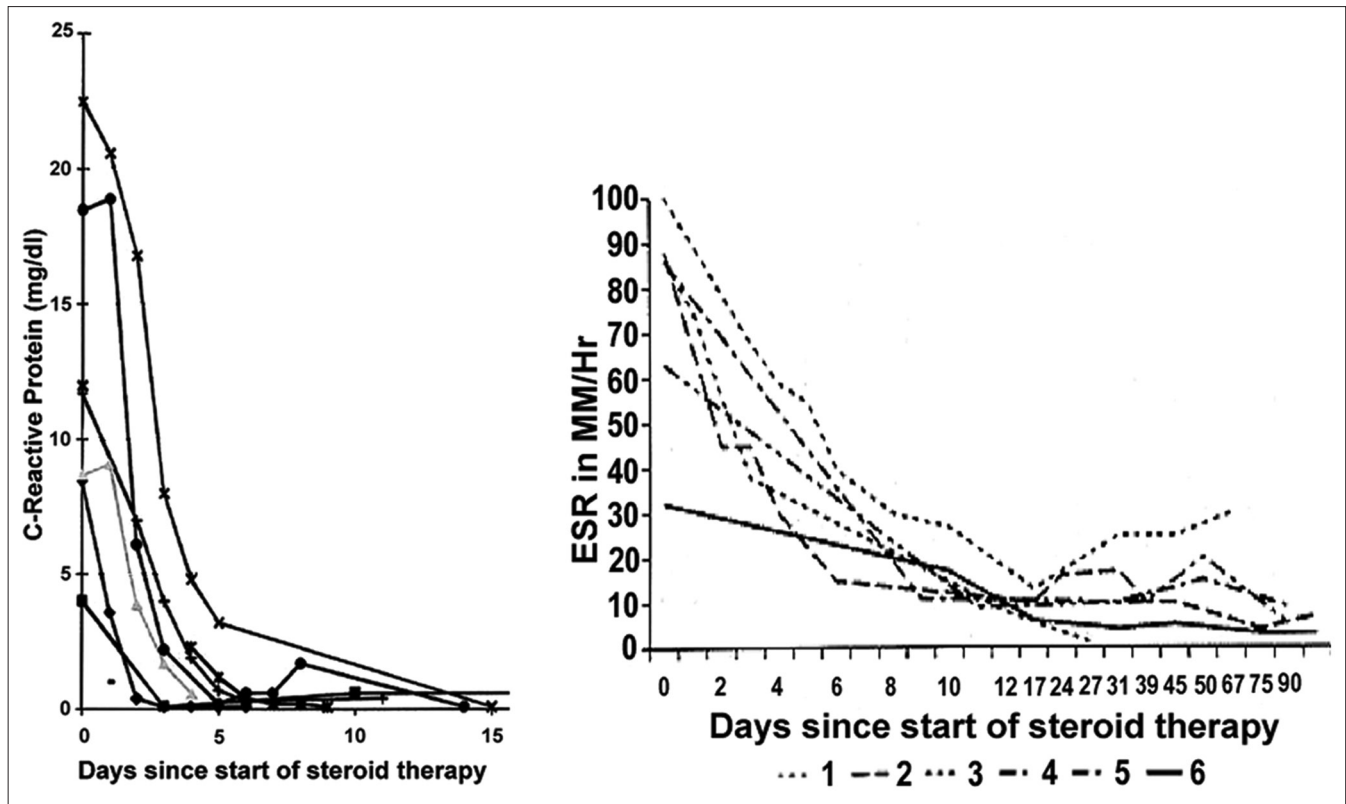
I developed GCA in early 2011. I have gone through the above prednisone therapy regimen, and have been on 1 mg Prednisone maintenance dose for years without any side-effects.

#### Alternate day corticosteroid therapy

This is proposed by some to reduce the risk of adverse reactions of corticosteroid therapy. But Hunder *et al.*<sup>[58]</sup>, based on a prospective study of GCA patients, concluded that alternate-day therapy is associated with a higher rate of treatment failure than is daily administration and that it does not satisfactorily control symptoms in most patients and cannot be recommended. My experience of dealing with about 300 GCA patients supports this view entirely.

#### Relapses of GCA on reduction of corticosteroid

Relapses or flare-up of symptoms on reduction or stoppage of corticosteroid therapy in GCA patients is reported commonly. This is due to *premature* reduction or stopping of the corticosteroid therapy. To prevent such relapses, the dose of corticosteroid therapy for GCA must be guided solely by



**Figure 9:** Graphs of C-reactive protein levels (left) and erythrocyte sedimentation rates (right) of six patients with GCA, showing their initial responses to high dose corticosteroid therapy

the levels of ESR and CRP, *NOT* by systemic symptoms. No cookie-cutter formula is effective.

#### Duration of corticosteroid therapy

Because of the frequent systemic side-effects of chronic corticosteroid therapy, the total duration of therapy in GCA is controversial. The view among rheumatologists is that it is reasonable to stop the therapy after 2 years, because they believe that GCA is a self-limited disease. That has not been my experience at all. I have found that most patients need a lifelong, small maintenance dose of corticosteroid therapy to prevent visual loss.

#### Is GCA a self-limited disease?

Rheumatologists believe that stopping steroid therapy after 2 years is reasonable because they believe that GCA is a self-limited disease, which burns itself within about 2 years.<sup>[59]</sup> My experience<sup>[54]</sup> showed that that is not true at all; repeat TABs have shown evidence of active disease, even after 9 years of corticosteroid therapy.<sup>[56,60]</sup>

#### Corticosteroid Resistant GCA

Rheumatologists often mention "corticosteroid resistant" GCA patients. My experience of more than five decades does not support that concept at all. I have had many patients referred to me by outside physicians with that diagnosis, who, when I treated them with adequate doses of corticosteroid, immediately responded to corticosteroid therapy. The basic reason for this misleading concept of "corticosteroid resistant GCA" is timidity, in using wholly inadequate doses of Prednisone.

#### Visual outcome after high-dose corticosteroid therapy

GCA patients being treated with high-dose corticosteroid therapy are anxious to find out whether there is going to be

visual improvement with treatment or further deterioration in spite of it.

1. We investigated this in GCA patients with visual loss.<sup>[61]</sup> Only 4% of eyes with visual loss due to GCA improved. The data also suggest that there is a better ( $P = 0.065$ ) chance of visual improvement with early diagnosis and immediate start of corticosteroid therapy.
2. In a study<sup>[57]</sup> of GCA patients, only 6% developed further visual acuity deterioration in one or both eyes within first 5 days after the start of therapy, and none after that. This showed that early, adequate corticosteroid therapy is effective in preventing further visual loss in most.

#### Side-effects of corticosteroid therapy in GCA

The invariable reason for giving GCA patients "too little, for too short a time" corticosteroid therapy is the common fear among physicians of the risks of dire systemic side-effects of corticosteroid therapy, particularly in the elderly.

Since 1965, I have treated several thousand patients with corticosteroid therapy, including about 300 with GCA and a large volume of those with ophthalmic rheumatological diseases (scleritis, uveitis, orbital myositis, retinal vasculitis) and ischemic optic neuropathies. Based on that knowledge, I have found that much of the apprehension among physicians about dire side-effects of corticosteroid therapy is totally unjustified provided the patients are followed closely for side-effects.

I have found a marked variation in the incidence and severity of side-effects with high dose therapy, varying from none at all to marked. As a GCA patient myself since 2011, I have been on corticosteroid therapy regimen (discussed above) since then;

while on high doses, the only side-effect I had was development of moon-face, which resolved completely on going to lower doses; I am still on maintenance dose, without any side-effect.

When I start a GCA patient on corticosteroid therapy, I discuss the pros and cons of the therapy, including various possible side-effects at length with the patients. I stress that if GCA patients are not treated with appropriate corticosteroid therapy, there is a high risk of blindness. So far, I have never seen any GCA patient refuse corticosteroid therapy. This is because fear of going blind is next to fear of death. I stress to them the importance of being followed closely for side-effects by their local physician, as well as in my clinic.

Prolonged oral corticosteroid therapy may be associated with side-effect such as osteoporosis, psychosis, peptic ulcer disease, infection, arterial hypertension, and diabetes mellitus. To prevent osteoporosis, supplementation with calcium, vitamin D, and bisphosphonate therapy is indicated. When stomach upset is present, initiation of a proton pump inhibitor or Histamine H2-receptor antagonist should be considered.

### Role of aspirin in management of GCA

Several studies have shown the presence of reactive thrombocytosis in GCA.<sup>[44]</sup> That has led some to assume that aspirin or other anti-platelet aggregating agents might have a role in the management of ischemic lesions in GCA. However, reactive thrombocytosis associated with GCA is not the same thing as essential thrombocytosis—the latter has a much higher platelet count and a high risk of thrombotic involvement of major vessels and the microcirculation. There is no convincing evidence that ischemic manifestations occur as a direct consequence of reactive thrombocytosis in GCA, particularly with the rather moderate increases in platelets. So there is little justification for giving aspirin or other platelet anti-aggregating agents to prevent visual loss in GCA. This subject is discussed at length elsewhere.<sup>[2]</sup>

### Corticosteroid sparing therapies in GCA

Since corticosteroid therapy is associated with systemic side-effects, there has been a constant search to find alternatives. The most common agent which has been advocated and studied is methotrexate. But two randomized, controlled, double-masked clinical trials of methotrexate found no corticosteroid-sparing benefit.<sup>[62,63]</sup> We did a preliminary randomized study of methotrexate in GCA, which showed no benefit. Others corticosteroid sparing agents include Imuran (Azathioprine), Cyclosporine A, Infliximab (Remicade), Enbrel (Etanercept), Adalimumab (Humira), Cyclophosphamide, Dapsone, Chlorambucil, and more recently Tocilizumab. I have discussed these therapies at length elsewhere.<sup>[2]</sup>

### Conclusion

If a patient older than 50 years presents with a history of amaurosis fugax, diplopia or sudden visual loss in one or both eyes, and has AION, PION, CRAO, cilioretinal artery occlusion or other acute ocular ischemic lesions, then the *physician must first rule out GCA by an immediate ESR and CRP evaluation - this is essential*. If there is a high index of suspicion of GCA from these and systemic findings, the patient should be started on high doses of systemic corticosteroid therapy without any delay. TAB should be done as soon as convenient to confirm the diagnosis, but the initiation of treatment must not wait for the biopsy results, because by that time, the patient may suffer further irreversible visual loss.

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### Conflicts of interest

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